ABSTRACT BOOK

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TO001

VERY ELDERLY ACUTE PROMYELOCYTIC LEUKEMIA: A MULTICENTRIC EXPERIENCE

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Background. Acute promyelocytic leukemia is a unique acute leukemia in terms of outcome. However, elderly population has limited therapeutic options due to biology of disease, performance status and presence of comorbidities. Recently, it is been published fairly good tolerance and efficacy with ATO+ATRA combination in elderly population, however there is still scarce information on very elderly (≥75y) that it might be underestimated in most registries as most physicians believe that is not worth to treat this AML subset population.

Objective. To analyze physicians' attitude in terms of treating this subgroup of very elderly APL population in the PETHEMA group and to analyze results in terms of efficacy and toxicity in patients who were treated according to PETHEMA trials between 1997 and 2017 compared with patients who received other strategies.

Methods. Selection of patients aged ≥75 years old with APL reported to PETHEMA registry over the last 19 years. Analyze epidemiologic characteristics and disease features in the very elderly APL population and describe percentage of patients treated according to investigators criteria. Analyze response rate in treated patients, percentage of induction deaths and OS. Statistical analysis was performed with R 2.14.0 software package.

Results. Between May 1997 and April 2017, 100 patients aged ≥75 years and demonstration of t(15;17) or PML/RARA rearrangement were reported to the PETHEMA registry. Median age was 78 (range, 75-90) years old, 50 were female, median ECOG was 2 (range, 0-4) and 20 (20%) patients were diagnosed with secondary APL. Sixty-four patients were treated with ATRA plus anthracycline-based regimens (42 according to PETHEMA trials), 20 with ATRA, 2 received other regimens (1 cytarabine and 1 cytarabine plus idarubicine) and 14 did not receive any treatment, except best supportive care. Characteristics of patients according to treatment (ATRA plus anthracycline-based schedule vs other strategies) can be observed in Table 1.

Table 1. Patients characteristics at diagnosis.

	AIDA (n=64)	Other strategies (n=36)	*p*
Age, years*	77 (75-84)	80 (75-90)	.001
Gender			ns
Male	30 (47)	20 (56)	
Female	34 (53)	16 (44)	
ECOG			<.001
0-1	30 (57)	6 (21)	
2-3	21 (40)	13 (45)	
4	2 (4)	10 (34)	
WBC (x10^9/L)*	1.5 (0.09-66.4)	1.36 (0.24-75.1)	ns
Hemoglobin (g/dL)*	9.1 (4.6-14.6)	8.8 (5,2-12.9)	ns
Platelets (x10^9/L)*	30 (3.7-208)	29 (1.5-132)	ns
Caryotype (n=64)			ns
t(15;17)	37 (79)	14 (82)	
t(15;17) and other abn	10 (21)	3 (18)	
PML-RARα isoform (n=63)			ns
1/2	29 (67)	11 (55)	
3	14 (33)	9 (45)	
Morfologic subtype (n=73)			ns
Hypergranular	50 (93)	16 (84)	
Microgranular	4 (7)	3 (16)	
Relapse Risk APL			ns
Low	22 (36)	8 (24)	
Intermediate	30 (49)	18 (55)	
High	9 (15)	7 (21)	

*median (range)

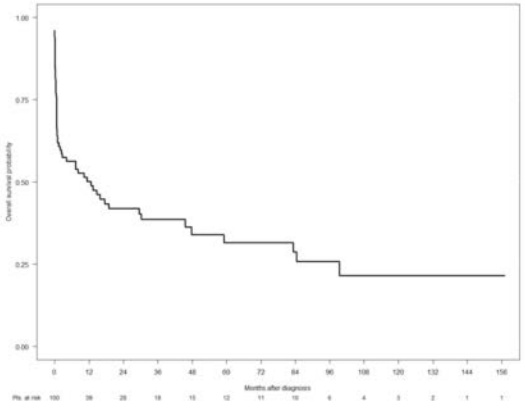

Figure 1. Overall survival in APL patients aged ≥75 years old.

In summary, both groups were statistically different related to age and ECOG. No other differences were found. Of those patients included in the first cohort, 71% (40 up to 56 with available data) achieved complete remission (CR) and 29% died during induction versus 36% (10 up to 28 patients) and 64%, respectively, in the

second group. No resistance was observed. Afterwards, relapse was observed in 6 patients, with a median time of 7 months (range, 4-16). The median follow.-up of patients included in this analysis was 27 months (range, 2-157). Median OS was 12 months and 2-year OS was 42% (Figure 1). One and 2-year OS in patients treated with AIDA regimens were 60% and 52% vs 33% and 22% of those who received other strategies (P<.001) (Figure 2).

Conclusions. Patients treated with ATRA plus anthracycline-based regimen showed better outcomes than patients who received other strategies. However, induction death in patients aged ≥ 75 years seems to be higher than it has been reported in younger patients.

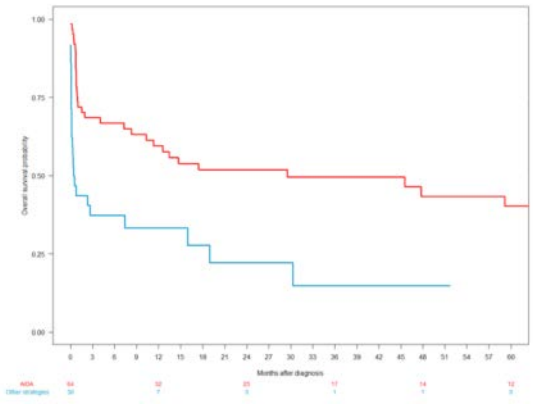

Figure 2. Overall survival in APL patients aged ≥75 years old according to treatment.

TO002
PROTHROMBINASE COMPLEX ASSEMBLY AND IN SITU FIBRIN DEPOSITION ON THE SURFACE OF ACUTE PROMYELOCYTIC LEUKEMIA CELLS

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Background. Early death due to hemorrhage still remains a major obstacle to achieving a complete cure for acute promyelocytic leukemia (APL). Disseminated intravascular coagulation (DIC) remains the main cause of consumptive coagulopathy contributing to hemorrhagic diathesis. However in contrast to DIC under other conditions, protein C, protein S and antithrombin levels are usually not decreased in APL, indicating only low grade DIC. Thus, it is attractive to speculate whether some unknown mechanism is depleting coagulation factors. We have shown that exposed PS on APL cells supports purified prothrombinase, but relatively little is known about the PS-driven prothrombinase complex assembly and in situ fibrin deposition on APL cells. Our objectives were to determine how APL cells promote thrombin generation and modulate fibrin formation and distribution, as well as to explore the relationship of in situ fibrin deposition and consumptive hemorrhage in APL patients.

Methods. Lactadherin was used as a probe for PS exposure on an immortalized APL cell line (NB4) and on the fresh APL blasts. PS exposure and fluorescein-labeled FV/VIII binding were evaluated by flow cytometry. Thrombin generation was measured by a modified thrombin generation test. Fibrin production was quantified by turbidity. The distribution of PS, prothrombinase complex and in situ fibrin deposition were explored using confocal microscopy.

Results. PS exposure increased approximately 6-fold after treatment with daunorubicin. All-trans retinoic acid and arsenic trioxide led to 70% reduction of PS exposure in 3 days and rose on day 3 and 5 (P<0.001), respectively. Level of externalized PS on APL cells paralleled level of FV/FVIII binding, lag time, peak thrombin, endogenous thrombin potential and fibrin formation. Lactadherin significantly inhibited the above parameters, while anti-tissue factor antibody or DNase I produced relatively minimal effects. Interestingly, confocal imaging showed that fibrin preferentially deposited on the surface of APL cells, which were defined as *in situ fibrin*. Untreated viable APL and NB4 cells displayed discrete or occasionally annular fibrin deposition on the membrane. Moreover, fibrin formation supported by apoptotic APL cells displayed a dynamic progress: (i) patchy deposition, (ii) diffuse rim, (iii) "fibrin coat", and (iv) network. The dynamic changes of fibrin formation paralleled the kinetics of PS exposure and prothrombinase assembly. Furthermore, initial percent of PS-positive fresh APL cells was negatively correlated with fibrinogen and factor II, V, VIII, and X of newly diagnosed APL patients (all P<0.01).

Conclusion. PS-driven prothrombinase complex assembly and in situ fibrin deposition on the surface of APL cells consume massive coagulation factors, providing a novel explanation for consumptive hemorrhage in APL patients. Blockade of PS might be a novel therapeutic approach for preventing bleeding in APL via inhibiting *in situ coagulation*, especially in high-risk APL.

Disclosure of Interest: None declared.

TO003
OVERVIEW OF PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA IN A DEVELOPING COUNTRY

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Background. Previous studies have suggested a variation in the incidence of acute promyelocytic leukemia (APL) among geographic regions with relatively higher percentages in Latin American population. A description of a pediatric cohort has not been explored in a developing country regarding clinical and molecular features presented at diagnosis. We aimed to describe an overview of pediatric APL (p-APL) assessing the frequency of RAS

pathway mutations and survival rates of Brazilian patients. Our goal is to provide insight into the distribution of clinical-demographic data and the molecular epidemiology potentially associated with APL development.

Methods. One hundred and forty-six p-APL cases (≤21 years old) were assessed throughout a multicentric study corresponding to 19.7% (146/742) of the de novo acute myeloid leukemia cohort (2000-2016). Diagnostic criteria included morphological and immunophenotypic features, and PML-RARa was detected by FISH and/or RT-PCR. Mutations in hotspot regions of FLT3, NRAS, KRAS, PTPN11, and KIT were identified. We also evaluated the risk association of GSTT1 polymorphism in case-case analysis and the effect of genetic susceptibility on overall survival. Patients were treated differently according to a period of incidence, with the inclusion of ATRA in the chemotherapy with anthracyclines and cytarabine. Kaplan-Meier survival analysis was used to calculate the 5-year probabilities of overall survival (5y-pOS), and estimated survival values were compared using the log-rank test. Cox proportional-hazard regression model with estimated hazard ratio (HR) and 95% confidence intervals (CI) were presented. Results. Patients were similarly distributed among age ranges >2-10 years old and >10-21 years old (47.3 and 50%, respectively), and no gender differences were observed. Four patients were aged ≤2 years old at diagnosis. Considering the mixed skin color remarkable of the population, patients were stratified as Black (10.5%) vs. Non-Black (90.5%). RAS pathway mutations were observed in 55.2% of cases, including FLT3 (44%), NRAS (7.3%), and KRAS (3.9%). Alterations in PTPN11 (rs61736914) and KIT (rs55789615) genes were represented by silent aminoacid substitutions (5.7% and 2.5%, respectively). Cases diagnosed among 2008-2016 presented a better outcome than those diagnosed in the first 8 years of the study (5y-pOS of 80.2±8.0% and 49.2±7.4%, p=0.004, respectively). Cases with high white blood cell (WBC) count ($>10\times10^9$/mL) presented poorer outcome than cases with low WBC count at diagnosis (5y-pOS 48.2±8.3% and 69.7±8.0%, p=0.006, respectively), as well as FLT3 mutations compared with wild-type cases (5y-pOS 35.2±12.8% and 68.6±7.4%, p=0.02, respectively). The presence of the GSTT1 null allele conferred adverse prognosis (HR 2.4, 95% CI 1.04-5.4, p=0.04). Conclusions. The disease-related death rate was slightly higher in Brazilian APL compared with those observed in developed countries. The diagnosis and management of APL raise questions that should be considered for further action. Specific clinical and molecular characteristics may stratify cases that could take advantage of an intensive therapy in this relatively homogeneous subtype of leukemia. GSTT1 polymorphism modified prognosis, suggesting that lower enzyme activity may play a synergistic effect with genetic alterations on modulating outcome.

TO004
COMBINING GENE MUTATION WITH GENE EXPRESSION DATA IMPROVES OUTCOMES PREDICTION IN ACUTE PROMYELOCYTIC LEUKEMIA

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In the context of all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy, heterogeneity on clinical outcomes of patients with acute promyelocytic leukemia (APL) may be higher than expected, mainly outside well-controlled clinical trials. Although recent clinical studies suggest that such heterogeneity could be significantly reduced or even abolished in light of the current arsenic trioxide (ATO)-based therapies, this compound is still not available for most reference centers in low- and middle-income countries (LMIC), and, at least for a near future, alternative strategies for predicting outcomes and improve risk stratification in APL should be tested. Here, we combined recurrent mutations with aberrant expression of genes previously associated with poor prognosis in both APL7-12 and acute myeloid leukemia (AML), and proposed an integrative score in APL (ISAPL) for outcomes prediction. As a learning set, dia-

gnostic bone marrow samples from 150 adult patients (median age: 34 years, range: 18-73 years) with newly diagnosed APL who were enrolled in the IC-APL study were analyzed. The treatment protocol was identical to that of the LPA2005 trial reported by the Programa Español de Tratamiento en Hematologia/Dutch-Belgian Hemato-Oncology Cooperative Group (PETHEMA/HOVON), except for the replacement of idarubicin by daunorubicin due to its better availability and lower cost in the participating centers. Integer weights for the risk score were derived from Cox proportional hazard model using OS as endpoint and including P-values lower than 0.05 in the model. Variables considered for the model inclusion were the follow: FLT3-ITD status, gene expression profile of ΔNp73/TAp73 ratio and transcript levels of KMT2E, BAALC, ID1, and WT1 genes. Other candidates, such as PIM2, PRAME, ERG, and IDH1 rs11554137 and WT1 rs16754 polymorphisms, were not associated with lower OS and not included in the score. Hazard ratios (HR) for OS were calculated for each variable separately. The HR was converted to integer weights according to the following: variables with HR < 1 were excluded from analyses; variables with HR > 1 and < 1.5 were assigned a weight of 1; variables with HR > 1.5 and < 2.5 were assigned a weight of 2; variables with HR > 2.5 were assigned a weight of 3. The final score was the sum of these integer weights.

Complete data for ISAPL modeling were available for 99 of 150 patients (median score: 5, range: 0-16). The median age of the learning set was 35 years (range: 18-65 years) with 44 males (44%). According to PETHEMA/GIMEMA criteria for predicting relapse,19 14%, 41%, 27% and 60% of patients assigned to the first, second, third and fourth ISAPL quartiles were deemed high-risk patients (p=0.036). Except for a higher leukocyte counts at diagnosis in patients assigned to the fourth-ISAPL quartile (p=0.033), no significant differences in baseline features were found among groups. Early mortality (p=0.005), complete remission (p=0.002), overall survival (pP<0.001), cumulative incidence of relapse (p=0.03), disease-free survival (p=0.017), and event-free survival (p<0.001) rates were significantly different among patients assigned to the first-, second-, third- and fourth-ISAPL quartiles.

In summary, ISAPL resulted in the separation of four distinct groups of patients, with significant differences for hematologic recovery, relapse, and survival. Next, we will validate these findings in an internal and external validation cohorts.

Oral Communications

CO001
THE RAR INTERACTOME: THE S100 CALCIUM BINDING PROTEIN A3 BINDS DIRECTLY AND SPECIFICALLY TO RAR AND PML-RAR AND MODULATE THEIR ACTIVITY IN ACUTE PROMYELOCYTIC CELLS

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RAR and the aberrant PML-RAR t(15:17) fusion product are the main retinoid nuclear receptors in acute promyelocytic leukemia (APL) blasts. RAR is also the major retinoid receptor expressed in acute myelogenous leukemia (AML) and various other types of solid tumors, including breast cancer. To define the RAR interactome, we initially used a breast cancer cell line genetically engineered to over-express an N-terminally tagged version of the nuclear retinoic acid receptor isotype. Using a differential proteomic approach involving quantitative SILAC mass spectrometry, we identified 17 nuclear proteins which interact with RAR and whose interaction is decreased by all-trans retinoic acid (ATRA). The majority of the 17 proteins are present in the histone fraction of chromatin. Among these proteins, HSP27, FABP5 and S100A3 stand out. The HSP27 heat shock protein and the S100A3 calcium binding protein have never been described to interact with RARs or any other member of the nuclear steroid receptor family. The interaction between RAR , HSP27, FABP5 and S100A3 was validated and confirmed by different types of co-immunoprecipitation experiments. Given the potential significance of S100A proteins in the control of the growth and differentiation of AML cells, we focused on S100A3 for further studies which were performed in COS-7 cells and the PML-RAR+ and APL-derived NB4 cell line. S100A3 interacts with RAR and PML-RAR in a selective fashion, as this calcium-binding protein does not interact with RAR , RARgamma or RXR . Over-expression cells of S100A3 in COS-7 exposed to ATRA increases the RAR and PML-RAR dependent transcriptional activity of the luciferase reporter gene controlled by the RARE 2 promoter. In the same experimental conditions, S100A3 stabilizes the RAR and PML-RAR proteins. All these results were validated in NB4 cells transiently over-expressing S100A3. On the basis of these data we generated three shRNA constructs targeting S100A3 in lentiviral vectors. NB4 cells were infected with the three shRNAs and corresponding scrambled controls generating different cell populations silenced for S100A3. In NB4 cultured under basal conditions, S100A3 silencing exerts only minor effects on the morphology and growth. Interestingly the basal expression of selected myelod differentiation markers, such as CD11b, CD11c and CD38 is significantly up-regulated in S100A3 silenced NB4 cells. In addition, ATRA-induced up-regulation of CD11b, CD11c and CD38 is enhanced by the knock-down of S100A3. These results are likely to be explained by the stabilization and increased dominant negative action of PML-RAR on the RAR protein. The results suggest that inhibition of S100A3 activity in APL blasts represents a viable option to potentiate the differentiating activity of ATRA and synthetic RAR agonists endowed with therapeutic potential.

CO002
WHOLE EXOME ANALYSIS OF RELAPSING PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Background. APL is, in the vast majority of cases, driven by t(15;17) translocation, which leads to PML/RARA rearrangement. APL is an uncommon genetically simple disease and only few additional alterations, cooperating with PML/RAR, have been described at diagnostic (Welch et al, Cell 2012). Most APL can be cured with targeted therapy combining all-trans retinoic acid (ATRA) and chemotherapy (CT). However, genetic mechanisms underlying the 10-15% relapses observed with this regimen remain unclear. The goal of the present study was to identify mutations that cooperate with PML/RAR and those responsible for acquired resistance to ATRA-CT treatment in APL patients by whole-exome sequencing of diagnostic/ remission/relapse trios.

Methods. Newly diagnosed APL patients included in clinical trials of the French Swiss Belgian APL group between 1994 and 2008, treated with ATRA-CT, before the introduction of first-line ATO, who experienced at least one relapse were studied. We collected retrospectively 64 samples from 23 patients, including 23 diagnostic samples, 18 at first complete remission (CR) and 23 at relapse (22 first relapse and 1 second relapse). Whole

exome-sequencing was performed on all samples. DNA libraries were prepared with the SureSelect human v5 kit (Agilent) and sequenced on Hiseq1000 (Illumina). The bioinformatic analysis was performed by GECO/integragen using CASAVA variant calling (Illumina) and dedicated pipeline. 18 trios and 5 duos passed the stringent quality control and were analyzed for somatic variants and copy number variations (CNV).

Results. After elimination of polymorphisms, the median number of somatic variants corresponding to de novo mutation at diagnosis was 14, while only 3 new somatic variants appeared at relapse (Figure 1). Notably, we failed to detect oncogene alterations other than PML/RARA in 7/23 (30%) patients. At diagnostic, 39% of patients (9/23) presented the common FLT3 alterations and at relapse 22% (5/23) of patients presented the known RARA mutations. Moreover, recurrent alterations were observed in activators of the MAPK signaling (22%): NRAS (2 patients), BRAF (1 patient), KRAS (1 patient), SPRY1 (1 patient). Mutations in the NT5C2 gene (3 patients), coding a 5'nucleotidase implicated in resistance to nucleoside-analog therapy, were solely observed at relapse, as in acute lymphoblastic leukemia (ALL). Abnormalities of epigenetic regulators were also detected at diagnostic and/or relapse: WT1 (7 patients, 30%), NSD1 (2 patients), TET2 (1 patient), ASXL1 (1 patient) and MED12 (2 patients). Homozygote WT1 inactivation by mutation plus neutral copy LOH occurred in 3 patients at relapse. The genetic markers identified allowed us to construct several evolution models. In 8 patients (35%), the diagnostic and relapse clones were clearly distinct, supporting the fact that they independently derived from pre-leukemic cells that survived ATRA/chemotherapy. In contrast, other relapses appeared to derive from the diagnostic clone.

Conclusions. Our data highlight the genetic simplicity of APL with very few alterations detected and 30% patients without identified mutations in addition to PML/RARa. Our results support the existence of two prototypic mechanisms of relapse: re-emergence of a new APL from persisting pre-leukemic cells and relapse from APLs often expressing strong oncogenes at diagnosis, impeding therapy response and favoring the acquisition of resistance mutations at relapse, including PML/RARA or NT5C2.

CO003
PML AND RARA MUTATIONS IN REFRACTORY ACUTE PROMYELOCYTIC LEUKAEMIA

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Acute promyelocytic leukemia (APL) is a distinct subtype of myeloid leukemia defined by the specific chromosomal translocation t(15;17), leading to the formation of PML/RARA fusion gene. Currently, the use of all-trans retinoic acid (ATRA) combined to anthracycline-based chemotherapy or alternatively, to arsenic trioxide (ATO), induces long-term remissions in at least 85% of APL patients. However, some patients still relapse after modern treatments and the mechanisms of resistance to ATRA and ATO still remain poorly understood. Recent studies have suggested that the presence of mutations in the two moieties of the oncoprotein PML/RARA may play a role in therapeutic response and outcome after ATRA and ATO. In addition, mutations in the unrearranged PML allele have been proposed as additional mechanisms linked to ATO resistance. We investigated the presence of PML mutations in 36 patients with de novo (n=31) or therapy-related APL (n=5), who received ATO as part of their treatment. We identified two ATO-resistant APL patients (UPN 25 and UPN 28), who presented a PML A216V mutation. In UPN 25, the PML A216V was present only in the PML/RARA hybrid, while in UPN 28 the same mutation was present both in the rearranged and unrearranged PML alleles.

The PML A216V is the most frequently reported mutation in PML-B2 domain and has been shown to confer resistance to ATO. Indeed, mutations of the PML-B2 domain of PML/RARA have been shown to affect the direct binding of ATO to PML, and therefore PML/RARA SUMOylation, disrupting its multimerization into nuclear bodies and its degradation. Mutations affecting the unrearranged allele of the PML gene seem to have similar effects, impairing nuclear bodies reformation, and inducing senescence in the surviving APL cells.

In addition, UPN 28 showed two mutations in the rearranged RARA gene. Both mutations are located in the ligand-binding domain (LBD) of RARA and have been shown to interfere with ATRA-binding capacity. In this patient, subclones with different combination of PML and RARA mutations may have acquired selective advantage during the disease course, probably leading to treatment resistance. Our study suggests that screening of PML mutations may help to identify ATO-resistant APL patients candidate to alternative treatment strategies. However, given the low frequency of these alterations, additional molecular mechanisms may be involved in treatment resistance and contribute to APL progression and relapse.

CO004
ARSENIC OVERCOMES RA-RESISTANCE CONFERRED BY FLT3-ITD IN A MOUSE MODEL OF APL

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Introduction. In acute promyelocytic leukemia (APL), the PML/RARA oncoprotein is sufficient to drive leukemogenesis. Experiments in mouse models have demonstrated that PML/RARA degradation is primary to the cure of APL with retinoic acid (RA) or arsenic (As) treatments. FLT3-ITD mutation occurs in almost 40% of APL cases and may confer a poorer prognosis. Reports have suggested that adding As to patients' treatment may abrogate this adverse effect.

Description. We used two transplantable models of

APL derived from different transgenic mice expressing either human (h)PML/RARA (referred to as P/R) or hPML/RARA-FLT3-ITD knock-in (ki) (referred to as P/R-FLT3 ki). The latter leukemic cells were obtained from a cross between two transgenic mice: an hPML/RARA and a FLT3-ITD ki breed. Mice were challenged with an intermediate dose of RA (10 mg) alone or with As. We examined APL cell differentiation, blast clearance, kinetics of PML/RARA degradation, and activated molecular pathways upon *in vivo* treatment.

In P/R-transplanted mice, granulocytic differentiation was observed starting from day 2 of RA treatment, whereas P/R-FLT3 ki-transplanted mice did not show features of cell differentiation until day 6. FACS analysis showed a strong and very early acquisition of differentiation surface markers (Gr1 and Mac) in P/R, while a delay was observed in P/R-FLT3 ki. Furthermore, on day 8 of RA treatment, no GFP-positive leukemic cells were present in the bone marrow of P/R-transplanted mice; the percentage of GFP-positive cells was up to 15% in P/R-FLT3 ki-transplanted mice. In parallel, loss of c-kit, a marker of leukemic cells, occurred on day 2 in P/R mice; however, it persisted until day 6 in the FLT3-ITD setting. RA induced rapid PML/RARA degradation, as assessed by immunofluorescence and immunoblotting in mice engrafted with P/R cells, while PML/RARA was still detected 8 days after treatment start in P/R-FLT3 ki.

We tested the combination of RA and As in mice. Cell differentiation was complete in the two APL models starting from day 2 of treatment. We noted a complete loss of GFP-positive leukemic cells at day 8 of treatment irrespective of FLT3-ITD status. This result correlated with rapid loss of c-kit at day 2 unlike that observed in RA-treated mice. PML/RARA degradation was accelerated by the combined treatment in P/R-FLT3 ki mice. In addition, combined RA/As treatment was associated with loss of clonogenicity of P/R-FLT3 ki APL in secondary recipients when compared with RA treatment alone.

Finally, we looked at the behavior of some RARA and p53 target genes upon 9- and 24-hour treatment with RA and/or As. Pai-1, a senescence gene, was found to be similarly and transiently 20-fold upregulated after RA treatment in both models. An even higher induction was observed with As only in P/R-transplanted mice. Lif (leukemia inhibitory factor) had remarkable short-term activation only in the absence of FLT3-ITD in RA and RA/As treatments. Unexpectedly, Cdkn1a, the p21-coding gene, appeared to be 5-fold and 2-fold upregulated in P/R and P/R-FLT3 ki mice, respectively, only after As was added to RA.

Conclusions. FLT3-ITD mutation impedes RA-induced loss of APL cells *in vivo*. Adding As to treatment overcomes the negative effect of FLT3-ITD on RA-induced phenotypes. Our results support the use of As as a first-line therapy in APL patients with a FLT3-ITD mutation.

CO005
MOLECULAR ANALYSIS OF THE INTERPLAY BETWEEN ALL-TRANS RETINOIC ACID AND HISTONE DEACETYLASE INHIBITORS IN ACUTE PROMYELOCYTIC LEUKEMIA CELLS

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Transcriptional repression is a characteristic feature of the leukemogenic process. In acute promyelocytic leukemia (APL), the fusion protein promyelocytic leukemia-retinoic acid receptor-α (PML-RARα) recruits transcriptional repressors to myeloid differentiation genes. All-trans-retinoic acid (ATRA) induces the proteasomal degradation of PML-RARα and granulocytic differentiation. Histone deacetylases (HDACs) fall into four classes (I-IV) and contribute to the transcription block caused by PML-RARα. Histone deacetylase inhibitors (HDACi) against Zinc-dependent HDACs (HDAC classes I, II, and IV) relieve transcriptional repression. HDACi act by a direct inhibition of HDACs and via a proteasomal degradation of PML-RARα. The E2 ubiquitin conjugase UBCH8 and the E3 ubiquitin ligases SIAH1/SIAH2 catalyze the latter process.

We set out to clarify the parameters that determine the molecular interplay between ATRA and HDACi against APL cells. To analyze differentiation and induction of apoptosis, we used immunoblotting, gene expression analyses, flow cytometry, and May-Grünwald-Giemsa staining. In these assays, we include drugs against class I HDACs (MS-275, VPA, and FK228), pan-HDACi (LBH589, SAHA), and the novel HDAC6-selective compound Marbostat-100.

We demonstrate that ATRA protects APL cells from cytotoxic effects of SAHA, MS-275, and Marbostat-100. However, LBH589 and FK228, which have a superior substrate-inhibitor dissociation constant (Ki) for the class I deacetylases HDAC1, 2, 3, are resistant against ATRA-dependent differentiation and the resulting cytoprotective effects. HDACi with superior Ki values can eliminate the differentiation-associated transcription factors C/EBPβ/ε and the mitochondrial apoptosis regulator B cell lymphoma (BCL)-xL in immature and differentiated NB4 cells. We further show that HDACi evoke cell cycle dependent DNA damage, measured as induction of phosphorylated histone H2AX and by the comet assay. ATRA can suppress DNA damage that is induced by SAHA, MS-275, and Marbostat-100, but it is ineffective with LBH589 and FK228. Thus, the induction of p-H2AX and the reduction of BCL-xL and C/EBPβ/ε are newly identified molecular markers for the efficacy of HDACi against APL cells.

We conclude that the affinity of HDACi for class I HDACs determines whether such drugs can kill naïve and maturated APL cells.

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CO006
MUTATIONS IN ACUTE PROMYELOCYTIC LEUKEMIA ARE SIMILAR AT DIAGNOSIS AND RELAPSE AND ETV6 MAY BE A MOLECULAR BIOMARKER OF DECREASED DISEASE-FREE SURVIVAL AND HIGH-RISK DISEASE INDEPENDENT OF WHITE BLOOD CELL COUNT

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Background. The risk of relapse-free survival (RFS) in patients with PML/RAR positive acute promyelocytic leukemia (APL) is defined based on white blood cell count (WBC) at presentation; patients with a WBC below or equal to10×10^9 are at low risk of relapse while those with a WBC over 10×10^9 are at high risk of relapse. Relapse risk drives treatment recommendations; current guidelines recommend ATRA/ATO combination therapy in patients with low-risk disease, and the incorporation of chemotherapy with ATRA in patients with high-risk disease. In this study we investigated 1) the mutational profiles of patients with APL at diagnosis and relapse 2) whether the mutational profiles of patients with a white count higher than 10×10^9 or lower/equal to 10×10^9 differed and 3) if relapse risk can be defined based on mutational profile, rather than WBC at diagnosis. Now that the majority of patients are cured, a marker more precise than WBC to identify the few patients who are likely to relapse, usually but not always, among high-risk patients, may be important.

Methods. After receipt of IRB approval, FLT3 mutational status was obtained from 195 patients. A subset of patients with banked DNA treated on US/North American Leukemia Intergroup group protocols E2491, C9710, had whole genome sequencing performed and linked clinical information was analyzed to assess relapse free survival based on white blood count at diagnosis, FLT3 positivity, and other mutational events.

Results. 195 patients had genomic DNA available for analysis of FLT3 mutational status, 82 from E2491 and 113 from C9710. At presentation, FLT3 was the most common co-occurring mutation, as described in previous studies. A subset of 45 patients had more extensive mutational profiling performed. Interestingly, 14 patients had mutations in genes encoding proteins that are part of the cohesin complex and 11 patients had mutations in genes involved with DNA methylation. When comparing 12 patients who had paired DNA available for analysis at the time of presentation and relapse, 7 had mutations in genes involved in DNA methylation at the time of diagnosis. At relapse, four patients retained the same mutations in methylation genes seen at diagnosis, one patient acquired new mutations and three reverted to a wild type state in methylation genes. FLT3-ITD was seen in 57% of patients with high risk disease versus 20% of patients with low risk disease ($p<.001$). The presence of a FLT3-D835 mutation did not differ statistically between patients with high risk and low risk disease. The presence of a FLT3 mutation was not predictive of worse outcome either in isolation or in combination with WBC over or equal to/less than $10x10^9$. However, there was a trend towards decreased disease-free survival in patients with a mutation in ETV6 ($p=.07$) that was independent of WBC at diagnosis.

Conclusions. The presence of a FLT3-ITD co-segregates with WBC over 10×10^9 in patients with APL, but does not by itself or in combination with WBC predict for decreased RFS. Mutations in genes involved in methylation and the cohesin complex are seen in patients with APL both at the time of diagnosis and relapse. Mutational profiles at the time of APL relapse are largely similar to those seen at the time of diagnosis, suggesting that a novel mutational event and clonal evolution does not drive relapse. However, ETV6 may predict a group of patients with decreased RFS, independent of WBC and may serve as a molecular biomarker of high-risk disease.

CO007
ACUTE PROMYELOCYTIC LEUKEMIA: MOLECULAR CHARACTERIZATION BY CANCER IMMUNE PROFILING MAY IDENTIFY PATIENTS AT RISK OF EARLY DEATH

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Background. APL is a highly curable malignancy with large co-operative group trials showing cure rates in excess of 90% and early mortality under 10%. Despite aggressive care, in the general population, 30% of patients die at presentation or shortly after initiation of treatment. Understanding the biology of the disease may help us identify the causes for these poor outcomes and allow for improvement in outcomes. Our study investigates the differences in expression genes involved in cancer immunology in APL patients with early mortality versus surviving patients.

Design. Archival blocks (n=3 alive and n=4 early death) with slides were retrieved, reviewed and clinical information obtained from patient charts under approved IRB protocol. Several patient/disease characteristics were identified including age, sex, race, body mass index (BMI), and cytogenetics were noted. Therapy indicators

such as treatment received, remission and relapse status was also noted. Seven 10 m sections of each case were used with >50% lesion. Total RNA was extracted from and analyzed with nanoString nCounter® using PanCancer Immune Profiling Panel designed to Perform multiplex gene expression analysis with 770 genes from 24 different immune cell types, common checkpoint inhibitors, CT antigens, and genes covering both the adaptive and innate immune response. and housekeeping genes. Following hybridization and data acquisition, we used Partek Genomics Suite® software for Robust Multi-array Average (RMA) normalization and to determine statistically significant differences in gene expression between experimental groups by ANOVA and pairwise comparisons (two-sided =0.05).

Results. The gene expression profiles of dead versus alive patients shows statistically significant (1.5 to 12X, p<0.05) downregulation of a set of 11 genes, and upregulation of 8 genes (p<0.05) (Figure 1). Although the role of these genes has not been studied in APL, they have been described in other tumors with the dysregulation of cancer immune escape showing a role in tumor suppression, differentiation, cell proliferation, chemo resistance and inflammation.

Significance. To the best of our knowledge, the current study represents the first cancer immune profiling exploration in understanding the early death in APL patients. Toll-like receptors (TLRs) play a vital role in activating immune responses. Activation of tumor cell TLRs not only promotes tumor cell proliferation and resistance to apoptosis. Previous studies have demonstrated that that prevention of interferon regulatory transcription factor 3 (IRF3) phosphorylation (along with interferon (IFN)-expression, STAT1 phosphorylation) is a critical downstream event in inhibitory effect of Arsenic trioxide (ATO) on Inducible nitric oxide synthase (iNOS) expression. This work is intriguing for the new information it provides about the cancer immune dysregulation of early deaths in APL.

Conclusions. We hypothesize that this dysregulation of cancer immune genes leads to a sustained proinflammatory state and also impart some resistance to an anti-inflammatory property of ATO that eventually leads to the poor outcomes. Further studies are needed to validate these results in a larger population and if confirmed can lead to better outcomes.

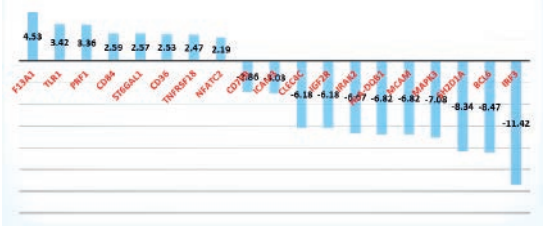

Figure 1. Differential gene Expression in APL patients early death *vs* alive.

CO008

EARLY DEATH AND OUTCOMES OF PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA USING ARSENIC AND RETINOIC ACID AS FIRST-LINE TREATMENT: A REAL WORLD STUDY

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Objective. We conducted a real world study of patients diagnosed with acute promyelocytic leukemia (APL) in our center in order to assess early death and outcomes using arsenic and retinoic acid as first-line treatment.

Methods. In this study, we evaluated the early death and outcome of 309 APL patients using arsenic and retinoic acid as first-line treatment in our center between 2005 and 2013. Low-, intermediate- and high-risk patients were defined according to Sanz sore based on the count of white blood cell and platelets at diagnosis. The early death was defined as death occurred within one month since induction treatment.

Results. The median age was 34 years old (2-82 years old). Children (<18 ys), adults (18-60 ys) and elderly (>60 ys) patients accounted for 15.2% (n=47), 80.9% (n=250) and 3.9% (n=12), respectively. The numbers of male and female patients were 172 and 137. Low-, intermediate- and high-risk patients accounts for 28.5% (n=88), 45% (n=139) and 26.5% (n=82). The median follow-up time was 78 months. The early death rate was 4.8% (n=15) and median death time was 8 days (range 1-29 days). The death causes was cerebral hemorrhage (n=9), lung hemorrhage (n=4), gastrointestinal hemorrhage (n=1) and respiratory failure (n=1). The early death rate showed a trend of decrease after 2008 (3.8% vs., 8.5% p=0.053). High-risk patients had a high early death than intermediate-or low-risk patients (15.8% vs. 1.4% vs. 0%, p<0.0001). For low-, intermediate- and high-risk patients, there was a similar cumulative incidence of relapse (2.3%, 9.5% and 4.4%, p=0.29) and disease-free survival (DFS) (96.6%, 95.5% and 94.2%, p=0.55), except for overall survival (OS) (97.7%, 95.4% and 80.3%, p<0.0001).

Conclusions. In this real world study, a relative low rate of early death was found under arsenic and retinoic acid as first-line treatment of APL patients. High-risk patients defined according to Sanz score hold a high risk of early death and OS but not relapse or DFS, which indicates the same post-remission treatment may be designed in future studies.

CO009
TREATMENT CENTER CHARACTERISTICS CORRELATED TO EARLY DEATH RATES IN PATIENTS WITH NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA: ANALYSIS OF THE U.S. SEER DATA

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Background. Acute promyelocytic leukemia (APL) is a unique subtype of AML with a high cure rate of 80-90% when treated with all-trans retinoic acid (ATRA)-based therapy. However, early death at presentation or during induction therapy due to hemorrhage remains the major cause for treatment failure. Using the Surveillance, Epidemiology, and End Results (SEER) data, we have previously reported an early death rate of 17.3% (Park J et al. Blood 2011;118:1248). We hypothesized that the early death may be associated with the expertise and availability of blood products at treatment centers and undertook a retrospective cohort study.

Methods. APL patients diagnosed between 1992 and 2009 in the United States were identified using SEER 13 data. Patients with available survival and treatment center information were eligible for the study. Early death was defined as death within one month of diagnosis. The treatment center information was obtained from the American Hospital Association database and included the following characteristics: number of hospital beds (<200, 200-500, >500), presence of intensive care unit (ICU), presence of blood bank and trauma center (as a surrogate indicator for availability of on-site blood products), and the teaching status (nonteaching, minor, major). Logistic regression was used to compare early death by selected hospital characteristics.

Results. The full-set of pre-specified treatment center information were available from six SEER 13 cancer registries (Iowa, Utah, Detroit, Connecticut, Hawaii, Seattle); from these registries, we identified 654 eligible patients of whom [182 patients (28%)] experienced an early death. Data on bed size (n=607), presence of ICU (n=578) and trauma center (n=567), and teaching status (n=654) were available in most patients. However, data on blood bank availability was only available in 312 patients but correlated to trauma center presence. Most APL patients were treated at centers with dedicated ICU (n=573, 88%) and ≥200 hospital beds (n=461, 70%), trauma center (n=385, 60%) and at teaching hospitals (n=433, 66%). Of the treatment center characteristics, analysis using logistic regression revealed that the presence of trauma center was statistically significantly associated with decreased probability of early death (odds ratio: 0.59, 95% CI: 0.39-0.91; p=0.02).

Conclusions. Early death remains the major cause of treatment failure in APL. Our data demonstrate an association of treatment center characteristics with survival in APL, and suggest a prompt referral of APL patients to a large treatment center with immediate access and availability of blood products may further improve the outcome of these patients.

CO010
EPIDEMIOLOGY, DIAGNOSIS, CLINICAL FEATURES AND OUTCOME OF ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS TREATED AT BATNA AGAINST CANCER CENTER IN ALGERIA

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Introduction. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia, represents 5 -15 % of them. APL is characterized by an accumulation of abnormal promyelocytes in bone marrow, a presence of t(15 ;17) translocation reciproque resulting in the fusion protein PML-RARα, a frequent coagulopathy netherthless highly curable currently with treatments strategies including differenciating agents: ATRA and ATO. We present a retrospective study spread over 8 years (January 2009 - December 2016), during which all the cases of APL are listed.

Patients, material and methods. Within the study period, 36 pts were diagnosed with APL based on morphological study of blood and medullary smear according to the FAB classification, infortunatly no cytogenetic study could be performed. All patients received ATRA plus chemotherapy, the epidemiological, clinical, biological and outcome features are reported.

Results. The 36 cases of APL represents 17,9% of the 210 AML, including 5 children (8 to 17 years) and 31 adults (18- 81).The median age is 34.5 years and sex ratio (M / F) was 0.89 (17 men and 19 women). Eight patients (22%) had familial cancer with 3 haematological cancer.

Bleeding syndrome was present at diagnosis in 29 patients (80%), anemia in the majority of patients (98%) and infectious syndrome in 28% of cases. According to Sanz score, 11 patients (30.55%) were high risk, 21 patients (58.33%) intermediate risk and 4 patients (11.11%) low risk. All patients received ATRA plus chemotherapy, in the end of 2016, 21 were still alive (58.33%) and 15 patients (41.66%) died, with 10 early death because bleeding (7pts with high leucocytes and 5 were over 70 years old). Only two patients relapsed.

The OS at 6 years is 58.3% : 43% in high risk and 57% in intermediate risk and 100% in low risk.

Discussion and Conclusion. APLs account for 18% of AMLs in our unit. We deplore the lack of cytogenetic or molecular study in our country. All the patients received ATRA and CT, howether early induction death was still high (26%) due to bleeding, the OS is 58% at 6 years must be improved.

CO011
PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA (APL) IN LATIN AMERICAN CHILDREN. IS IT POSSIBLE TO WORK TOGETHER? THE CLEHOP INITIATIVE

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Background. Cancer in children is a rare disease of high social and financial cost; differences in regional survival rates result from missing diagnostic and/or therapeutic opportunities. In Latin America and the Caribbean 17.500 new cases of childhood cancer are diagnosed each year resulting in more than 8.000 deaths per year. The idea of working coordinately in Latin America arose in 2013, leading to the creation of a Latin American Consortium for Pediatric Hematology and Oncology (CLEHOP), with the purpose of facilitating a cooperative effort to improve the cure rate of children with cancer. The consortium is composed of regional (AHOPCA, Central America) and National (GATLA, Argentina; PINDA, Chile) Groups, as well as local centers of Brazil, Colombia, Peru, Mexico and Venezuela.

Methods. CLEHOP has focused its activities on Acute Promyelocytic Leukemia (APL) because of its distinct epidemiological characteristics. Population from Latin America have a higher incidence of APL and in some geographic areas a distinct distribution of the PML-RARA isoforms. Compared to North America, the assessed APL risk among AML cases was more than two times The majority of centers in Latin America adopted protocols based on ATRA plus Anthracyclines, similar to those reported by the Italian GIMEMA or the Spanish PETHEMA groups. However, a major concern is the cost of treatment in our countries.

Results. On December of 2016 CLEHOP with the support of St Jude Children's Research Hospital (Global Medicine Department) and Italy began to work on a trial for pediatric APL treatment. This new trial should be feasible in the different countries. Given that we have different resources and access to drugs, we decided to stratify the APL regimen in two risk groups according leucocyte count and designed different arms of treatment: 1) Induction with anthracycline and ATRA, three blocks of consolidation and maintenance vs 2) Induction with ATRA/ATO plus anthracyclines depending on the risk followed by consolidation.

Conclusions. We think that it is possible to launch this protocol in our countries in the next few months. This structured network will permit us to accrue a large number of patients, to share experiences and to conduct a cooperative international study which could lead to a substantial improvement of the treatment of APL in the whole continent.

CO013
RETINOIC ACID AND ARSENIC TRIOXIDE SENSITIZE ACUTE PROMYELOCYTIC LEUKEMIA CELLS TO ER STRESS

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Promyelocytic leukemia (APL) is characterized by the chromosomal translocation t(15:17) that results in the expression of the chimeric protein PML-RARα. The fusion of PML, a tumor suppressor that is the major component of the PML-nuclear bodies, with the Retinoic Acid Receptor-α arrests the differentiation program driven by RARα, blocking the leukemic blasts at the promyelocytic stage. Pharmacological doses of Retinoic Acid (RA) are able to remove the block, resume granulocytic differentiation and partially degrade PML-RARα leading to reformation of nuclear bodies. The association of RA with chemotherapy or with arsenic trioxide (ATO), the latter efficiently targeting PML-RARα for degradation, results in high cure rates of acute promyelocytic leukemia (APL). Despite showing a considerably improved safety profile, either RA or ATO are not devoid of toxicity, with the most important and potentially life-threatening one being the so-called retinoic acid differentiation syndrome. We show here that RA-induced differentiation of human APL cell lines and primary blasts dramatically increases their sensitivity to ER stress inducing drugs, like Tunicamycin (Tm), at doses that are not toxic in the absence of RA. Importantly only human progenitors cells derived from APL patients resulted sensitive to the combined treatment with RA and Tm whereas those obtained from healthy donors were not affected. Granulocytic differentiation of APL cells driven by RA triggers a physiological Unfolded Protein Response, a series of pathways emanating from the ER in case of ER stress, which ensues when higher protein folding activity is required as during differentiation. Although mild, the ER stress induced by RA is sufficient to render differentiating APL cells very sensitive to low doses of Tm. We also show that the UPR pathway downstream of PERK plays a major protective role against ER stress in differentiating cells and, by using a specific PERK inhibitor, we potentiated the toxic effect of the combination of RA and Tm. Moreover we found that low amounts of pharmacologically induced ER stress are also able to strongly increase ATO toxicity even in the absence of RA. Indeed the combination of ATO with Tm efficiently induced apoptosis in RA-sensitive and

RA-resistant APL cell lines, at doses ineffective in the absence of ER stress. Eventually, we demonstrate that insurgency of oxidative stress, tightly linked with the UPR, is at the basis of the toxicity induced by Tm in combination with RA and/or ATO. In conclusion, our findings identify the ER stress-related pathways as potential targets in the search for novel therapeutic strategies in AML.

CO014
PML/RARA INTERFERES WITH NRF2 FUNCTION IN ACUTE PROMYELOCYTIC LEUKEMIA CELLS

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Nrf2 (NF-E2 p45-related factor 2) mediates adaptive responses to stress and its expression and subcellular location is regulated by a complex network that enhances Nrf2 activation during redox perturbation, inflammation, growth factor stimulation and nutrient/energy fluxes. We previously demonstrated that high doses of ascorbic acid (ASC) selectively kill leukemic blasts from patients with acute promyelocytic leukemia (APL). PML protein acts as a stress sensor and minimizes the reactive oxygen species (ROS) damage. In normal cells, loss of PML is involved in regulating abundance, stability and nuclear accumulation of Nrf2 by modulating ROS production. PML directly facilitates ROS scavenging and inhibits nuclear accumulation and trans-activation of Nrf2 both in the cytoplasm and in PML-nuclear bodies (NBs). We aimed at investigating here how the APL-unique PML/RARA oncoprotein affects the Nrf2 pathway. Quantitative RT-PCR was used to assess the expression levels of 3 Nrf2 target genes: HO-1, NQO-1 and AKR1C1 in 13 primary samples from APL patients. The mean transcript copy number values were 1.7±1.8; 10.5±9,8 and 0.25±0,37 for HO-1, NQO-1 and AKR1C1 respectively, compared to 30,6±30.2; 44±46 and 0,9±1.8 detected in 12 non-M3 AML diagnostic samples (p=0.0007; p=0.0016 and p= 0.005). The mean value of the same gene transcripts in 5 normal bone marrow samples were 1,6±1.8; 1.1±0.5 and 1.0±0.3, respectively. Immunofluorescence experiments carried out in a PML/RARA inducible system (PR9 cell line), revealed that the localization of Nrf2 was mainly nuclear and mostly localized in nuclear bodies (NBs) in untreated and non-induced cells. Nrf2 was exported from the nucleus into the cytoplasm 8 hours following induction of PML/RARA, with consequent reduction of its activity as indicated by a significant decrease of HO-1 Nrf2-induced protein expression (PR9 cells + Zn: 1.8±0.6, vs Bulk ctrl cells + Zn 42.6±3,6 at 6 hours, p=0.003). Subcellular localization of Nrf2 was also confirmed by Western Blot analysis on both cytoplasmic and nuclear cell fractions. Nrf2 actually increased in the nuclear fraction in control cells, lacking PML/RARA, while Nrf2 accumulated in the cytoplasm in PR9 PML/RARA+ve cells. Together, these results show that the Nrf2 protein is exported to the cytoplasm following PML/RARA expression and PML NBs disruption, suggesting a molecular link between reduction of Nrf2 transcriptional activity and PML/RARA expression.

CO015
MOLECULAR ANALYSIS OF ACUTE PROMYELOCYTIC LEUKEMIA BY NEXT GENERATION SEQUENCING

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Introduction. The recent advent of next-generation sequencing (NGS) technologies has allowed the discovery of a growing number of novel mutations in acute myeloid leukemia (AML). However, most of the projects are focused on AMLs other than acute promyelocytic leukemia (APL). Thus, although it is known that APL exomes usually present non-recurrent mutations that could cooperate with the PML-RARA fusion protein to promote the leukemic transformation, the mutational spectrum of APL is still unknown. The aim of this study is to analyze the mutational landscape of de novo and secondary APL with NGS and compare it with that of other favorable acute myeloid leukemias.

Methods. The study included 24 APL patients (17 de novo and 7 secondary) and 28 non-APL favorable risk patients (13 CBFB-MYH11, 15 AML1-ETO). We used the Ampliseq AML panel on a PGM platform; this panel analyzes 19 myeloid genes: ASXL1 (exon 12), BRAF (V600E), CBL (exons 8-9), FLT3 (codons 676, 830-850), IDH1 (exon 4), IDH2 (exon 4), JAK2 (exon 14), KIT (exons 8, 10, 11, 17), KRAS (exons 2,3,4), NRAS (exons 2,3,4), PTPN11 (3,7,8,13), RUNX1 (exons 3-8) and WT1 (exons 7 and 9) and the whole coding sequence of DNMT3A, GATA2, TET2 and TP53. FLT3-ITD mutations were analyzed by genescan.

Results. Mean coverage was 3,064X, and mean mapped reads per sample was 801,402. Mean uniformity and on-target was above 90%. Using NGS, 8 out of 24 (33.3%) APL patients showed at least one mutation. The most frequently mutated genes were FLT3 (45,8%), WT1 (29.2%) and TET2 (20.8%), followed by NRAS (12.5%) and RUNX1 (8.33%). Only one patient (4.1%) harbored mutations in CBL or GATA2. None of the mutated genes were mutually exclusive with each other nor were associated with the PML-RARA transcript type. We did not find mutations associated with secondary or de novo APL. Considering all the favorable group, the mutation distribution per gene was different between APL and other favorable risk patients. Mutations in JAK2 or KRAS were found only in non-APL favorable leukemias

whereas FLT3 and WT1 were more frequent in APL. However, all the favorable group shared the same mean number of mutations and the absence of mutations in DNMT3A, IDH, BRAF or PTPN11. (Figure 1A).

Variant allele frequency ranged from 2.24 to 73.2%. WT1 mutations showed the most disperse range, while RUNX1 mutations showed a VAF around 50%, suggesting a potential germ line origin (Figure 1B).

Conclusions. Our data suggest that APL patients could harbor mutations in recurrent myeloid genes, mainly FLT3, WT1, TET2 and NRAS. Mutations in genes involved in signaling processes are usually found at a low VAF in other types of leukemia and patients harboring them could benefit of combined targeted therapy. We are working on further research in order to understand the involvement of these mutations in APL clinical management.

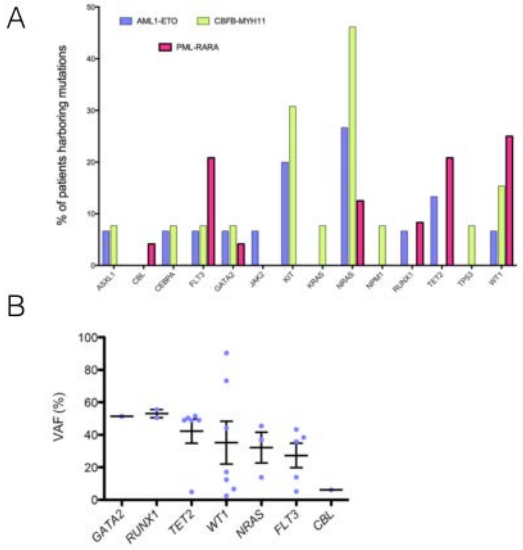

Figure 1.

CO016
METABOLIC CATASTROPHE OF ARSENIC TRIOXIDE RESISTANT CELLS IN ACUTE PROMYELOCYTIC LEUKEMIA

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ATO resistance in acute promyelocytic leukemia (APL) has centred on mutations in PML-RARA gene (Blood 2011, NEJM 2014). However such mutations are rare and cannot explain the majority of relapses seen in the clinic. To evaluate the mechanisms of ATO resistance, we used in-house generated ATO-resistant NB4 subclone NB4-EVAsR1 (A216V – VAF-91.7%) along with another ATO-resistant promyelocytic cell line (UF1) which does not have the A216V ATO resistance-conferring mutation. In a gene expression array, it was evident that the redox signalling, AMPK signalling and energy metabolism pathways were significantly dysregulated in the ATO-resistant cell lines compared to naïve NB4 cells.

Towards validating the microarray data and to characterise the ATO-resistant cell lines we measured the basal levels of reactive oxygen species (ROS), glutathione (GSH), mitochondrial membrane potential (MMP), autophagy and glucose uptake in comparison to naïve NB4 cells. We observed that the ATO-resistant APL cell lines are metabolically distinct from the ATO sensitive naïve NB4 cells and also showed cross-resistance to other conventional chemotherapeutic agents such as daunorubicin hydrochloride and cytosine arabinoside. In order to further dissect out the metabolic dependency of the resistant cells, we evaluated their sensitivity to a glycolytic inhibitor as it's been reported that the malignant cells rely on "Warburg effect". Treating the cell lines with a glycolytic inhibitor (2-deoxy glucose -2DG) alone or in combination with ATO demonstrated that the resistant cell lines were not relying on glycolysis for cell survival and proliferation in contrast to naïve NB4 cells (Figure 1a).

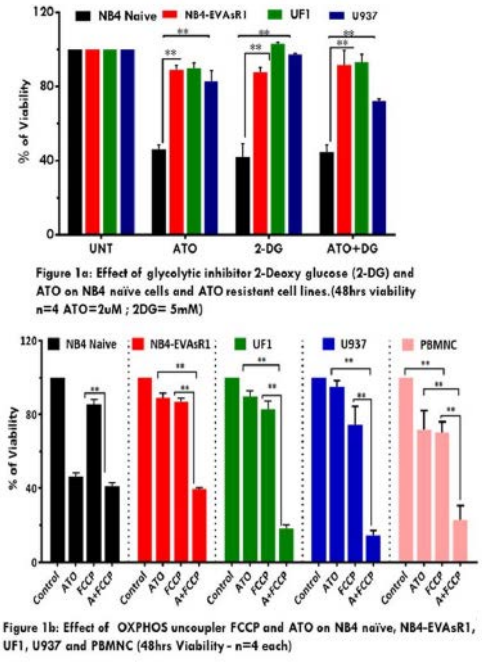

Figure 1.

We then evaluated the effect of mitochondrial oxidative phosphorylation (OXPHOS) inhibitor on these cell lines. We anticipated that the resistant cell lines viability would be significantly affected byFCCP (an uncoupler of OXPHOS) treatment since they were not relying on Warburg effect. However, we observed that the viability of the resistant cell lines still remained unaffected whereas when we combined FCCP with arsenic trioxide, the combination significantly reduced the viability of resistant cell lines. The combination not only reduced the sur-

vival of ATO-resistant promyelocytic cells but also the innate ATO-resistant myeloid and lymphoid leukemic cells such as U937, THP-1and Jurkat E6.1 (Figure 1b). We also noted that there is a significant bystander effect on the normal peripheral blood mononuclear cells (Figure 1b).We conclude that the resistant cell lines have the ability to switch between the two energy-producing pathways efficiently when one is inhibited (Figure 2). Further strategies include the screening of compounds selectively targeting the malignant cell's metabolism sparing the normal cells in combination with arsenic trioxide which has the potential to be translated into the clinic. There is a number of FDA approved molecules widely used in the clinic and are reported to have OXPHOS uncoupling activity. This data also draws attention to the possible severe systemic off-target toxicity of such compounds in combination with ATO which may be inadvertently used in the clinic.

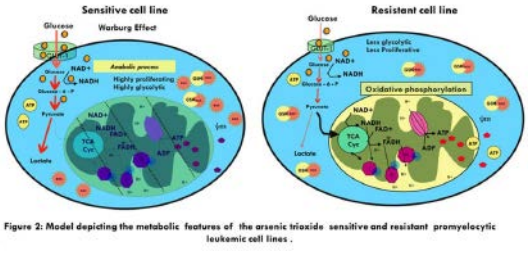

Figure 2: Model depicting the metabolic features of the arsenic trioxide sensitive and resistant promyelocytic leukemic cell lines .

Figure 2.

CO017

CLINICAL SIGNIFICANCE OF COMPLEX KARYOTYPE AT DIAGNOSIS IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH ATRA AND CHEMOTHERAPY BASED PETHEMA TRIALS

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Some large studies have showed the lack of prognostic impact of additional chromosome abnormalities in patients with t(15;17) APL treated with ATRA and chemotherapy-based front-line therapies. However, recent reports suggested that the presence of a complex karyotype (i.e, 2 or more additional abnormalities) was related with a higher relapse rate in patients treated with ATO+ATRA regimens. We aim to further investigate whether a complex karyotype could be related with a higher relapse incidence in APL patients treated with PETHEMA trials.

Materials and methods. Between 1996 and 2012, 1559 consecutive adult and pediatric patients were enrolled in the PETHEMA LPA 96, 99 and 2005 trials from the PETHEMA, HOVON, GATLA, and PALG groups. Cytogenetic analyses in bone marrow samples at diagnosis were performed in local laboratories. Cytogenetic reports were available in 1128 patients (72%) (the remaining patients lacked of data or had unsuccessful analysis/no growth). Treatment consisted of Induction therapy with oral ATRA (45 mg/m^2/d) and intravenous idarubicin (12 mg/m^2/d x4 days) followed by three courses of consolidation with anthracycline monochemotherapy. In the PETHEMA 99 trial ATRA was added in each cycle of consolidation for intermediate and high risk patients, according to Relapse-risk score. Ara-C was added in consolidation for high-risk patients in the LPA2005 trial. In all trials, maintenance therapy consisted of intermittent ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurine.

Results. Overall, 842 patients (75%) showed no additional abnormalities (i.e, normal karyotype or single t(15;17)), 197 patients (17%) showed 1 additional abnormality, and 89 patients (8%) had a complex karyotype (2 or more additional abnormalities, of them 41 (4%) had 3 or more additional abnormalities). The only clinical or biological characteristic associated with a complex karyotype was CD34 antigen negativity in leukemic blasts (p=0.04). There was not a higher induction death rate in patients with a complex karyotype. The 5-year overall survival was not different between patients with complex karyotype (2 or more additional abnormalities) and those with no or 1 additonal abnormality (83% vs 84%, p=0.56), while the 5-year cumulative incidence of relapse was 18%, compared with 12% (P=0.09). However, the CIR at 5 years was higher among patients with 3 or more additional abnormalities (27% vs 12%, p=0.003). In the multivariate analysis, the presence of 3 or more additional abnormalities retained the statistical significance (p<0.0001), together with higher relapse-risk score (p<0.001), male gender (p=0.008), and PETHEMA LPA96&99 trials (p=0.05). This study shows, for the first time, an increased risk of relapse among patients with very complex karyotype (at least 3 additional abnormalities) among APL patients treated with ATRA plus chemotherapy front-line regimens. It should be noted that only 4% of patients with an evaluable cytogenetics had a very complex karyotype.

CO018
DIFFERENTIAL EXPRESSION OF TISSUE FACTOR F3 AND NUCLEAR RECEPTORS 4A IN EARLY DEATH ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS

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Introduction. Although patients with acute promyelocytic leukemia (APL) have a favourable prognosis, 5-10% suffer an early death (ED) within 30 days, due to infections as well as haemorrhagic and thrombotic complications. Though different risk factors could be identified, the underlying mechanisms are unclear and successful treatment of ED in APL patients could not be achieved so far (Kwaan *et al*., 2014, Lehmann *et al*., 2017). For this reason, it is highly important to identify novel factors implicated in the mechanistic processes in ED APL patients.

Methods. To identify target genes, 50 bp single-read RNA sequencing (RNAseq) of 6 ED and 9 APL controls (cohort 1; n=15) and 4 ED and 5 APL controls (cohort 2; n=9) was executed. Samples were taken from patients with confirmed diagnosis of APL before beginning of treatment. Cohort 1 consisted of 7 female and 8 male patients with a median age of 60 years (range 37-73 years). According to the Sanz score depending on leukocyte and platelet counts, 10 patients were in the high-risk group and 5 patients were in the low/intermediate-risk group. Patients of cohort 1 were treated according to the AIDA2000 protocol of the Study Alliance Leukemia (SAL) study group. Cohort 2 consisted of 3 female and 6 male patients with a median age of 55 years (range 36-79 years), of which 4 patients were in the high-risk group and 5 patients were in the low/intermediate-risk group. Most patients of cohort 2 were treated according to the AIDA2000 (SAL) or APL0406 protocol. Gene validation was performed via RT-qPCR. PML-RAR variants were determined by Mentype AMLplexQS (Biotype). PML-RAR bcr1 or bcr3 variants were overexpressed in U937 cells engaging Amaxa nucleofector technology. NB4 cells were treated with 1 μM all-trans retinoic acid (ATRA) for 72 h. In silico survival analyses of AML patients were evaluated via SurvExpress (Aguirre-Gamboa *et al*., 2013).

Results. RNAseq of cohort 1 showed F3 (Coagulation Factor III, Tissue Factor) downregulated in ED compared to control APL cases. GSEA analysis further identified a gene family including F3 and members of nuclear receptor 4A family, NR4A1/2/3, co-regulated upon leukotriene and thrombin treatment. Downregulation of all four factors could be validated by RT-qPCR or RNAseq of cohort 2. In silico analyses further showed significantly decreased survival of AML patients with low expression of F3, NR4A2 or NR4A3. Interestingly, treatment of NB4 cells with ATRA caused further downregulation of F3 but upregulation of NR4A2 and NR4A3. Analysis of PML-RAR variants in APL control and ED cases (n=40) showed a significant enrichment of the short variant bcr3 in ED APL. Overexpression analyses of the short bcr3 and long bcr1 PML/RAR variant in U937 further showed a correlation between bcr3 and downregulation of NR4A1/2/3.

Conclusions. Expression of F3 and NR4A1/2/3 is downregulated in APL ED and decreased expression of NR4A1/2/3 is associated with short PML-RAR variant bcr3, which is significantly enriched in ED APL. Since NR4A members are associated with coagulation and inflammation, they may be important F3-related factors, contributing to the bcr3 ED APL phenotype. Moreover, NR4A2/3 expression can be induced by ATRA treatment, which may have therapeutic implications for other AML subtypes with reduced levels of these nuclear receptors.

CO019
THE IMPACT OF ORAL ARSENIC AND ALL-TRANS-RETINOIC ACID ON COAGULOPATHY IN ACUTE PROMYELOCYTIC LEUKEMIA

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Objective. The aim of our study was to evaluate the impact of oral arsenic (the realgar-indigo naturalis formula, RIF) and all-trans retinoic acid (ATRA) on coagulopathy in acute promyelocytic leukemia (APL) compared with intravenous arsenic trioxide (ATO) plus ATRA during induction.

Methods. D-dimer levels, prothrombin time (PT), fibrinogen (Fbg) levels and the platelet count were comparably analyzed among 83 newly diagnosed APL patients treated with different induction regimens of RIF (n=45) or with ATO (n=38). The recording time points were respectively set at the first visit (day 0) and after treatment (day 4, day 7, day 10, day 14, day 17, day 21 and day 28).

Results. Since induction therapy with RIF and ATRA, the median levels of Fbg, PT and platelets were recovered to the normal range within 4 days, 10 days and 28 days, respectively. The last day of platelet and plasma transfusion was day 12 (range: 0-24 days) and day 3 (range: 0-27 days), respectively.There were no differences in the platelet recovery and coagulopathy correction after RIF and ATO treatment. Among the 42 patients with a disseminated intravascular coagulation (DIC) score =4, the consumption of transfused platelets was less in theRIF group than that in the ATO group (p=0.037).In the 17 patients with a DIC score 4, prompt recovery of Fbg levels (P=0.028) was observed in theRIF group compared with that in the ATO group (p=0.401).

Conclusions. RIF and ATRA therapy amelioratecoagulopathy rapidly in APL patients. RIF shows a significant beneficial effect in accelerating the recovery of thrombocytopenia and hypofibrinogenemia forsubclinical DIC patients.

CO020
TOXICITY IN PEDIATRIC PATIENTS TREATED WITH ALL-TRANS RETINOIC ACID AND ARSENIC TRIOXIDE INDUCTION: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP STUDY AAML1331

Kutny M, Alonzo T, Gerbing R, Wang Y, Fu C, Meshinchi S, Raimondi S, Hirsch B, Rajpurkar M, Abla O, Sung L, O'Dwyer K, Howell D, Sun W, Kahwash S, Kolb E, Feusner J, Gregory J

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Recent studies demonstrate that all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) with minimal or no chemotherapy are safe and effective for adults with acute promyelocytic leukemia (APL), but similar data on pediatric patients are limited. The Children's Oncology Group (COG) trial AAML1331 is currently enrolling patients to test an ATRA/ATO-based regimen. The objective of this interim analysis is to describe the toxicities and tolerability of ATRA/ATO induction in pediatric APL patients.

Eligibility criteria included age 1-21.99 years, diagnosis of de novo APL, and PCR-confirmed t(15;17). ATRA was started at first suspicion of APL, with a maximum 5 days of pretreatment allowed before additional induction therapy. Risk group was determined by diagnostic white blood cell (WBC) count: standard risk (SR) WBC<10,000/μL and high risk (HR) WBC≥10,000/μL. Herein, we report only the interim induction toxicities. Induction therapy was as follows: all patients received ATRA 12.5 mg/m^2/dose twice daily (dosed according to observed BSA without adjustment for obesity) and ATO 0.15 mg/kg daily for minimum of 28 days and until hematologic complete response (up to 70 days); HR patients also received idarubicin 12 mg/m^2 4 doses on days 1, 3, 5, 7 and dexamethasone 2.5 mg/m^2/dose twice daily on days 1-14. SR patients received dexamethasone only if WBC rose to >10,000/μL (hyperleukocytosis). SR patients with hyperleukocytosis also received hydroxyurea at 30 mg/kg/dose (maximum 1000 mg/dose) 4 times daily. Patients with symptoms of differentiation syndrome (DS) had their ATRA/ATO held and dexamethasone administered at 5.8 mg/m^2/dose (maximum 10 mg/dose) IV twice daily for at least 3 days or until resolution of DS.

This interim analysis included 63 evaluable patients (47 SR and 16 HR) as of March 31, 2017. Hyperleukocytosis developed in 14% of SR patients (6/43; data missing for 4) with median maximum WBC of 54,350 (range 22,000-95,700). Two (33%) patients with hyperleukocytosis developed DS, which was similar to the 22% (8/37) DS rate in SR patients without hyperleukocytosis (p=0.6). Overall, DS occurred in 25% (16/63) of patients, with similar rates in SR and HR groups (p=1.0). DS occurred at a median of 2.5 days (range 0-18) (Figure 1). We monitored 12 common signs/symptoms of DS, and those seen in at least 50% of patients with DS were respiratory distress (n=10), fever (n=10) and weight gain (n=9). Life threatening events were less common: pleural effusion (n=4), pericardial effusion (n=2), and acute renal failure (n=2), and no cases of congestive heart failure. Other than DS, doses of ATRA, ATO, or both were held due to pseudotumor cerebri (n=4), AST/ALT elevation (n=6), C difficile colitis sepsis (n=1), acute kidney injury (n=1), and respiratory distress/chest pain (n=1). In most patients, doses were held for ≤3 days, but in some they were held for >7 days due to DS or elevated AST/ALT. One SR APL patient died during induction therapy due to complications of coagulopathy, DS, and enterococcal sepsis. Our initial experience with ATRA/ATO during induction for pediatric patients treated in AAML1331 shows that this regimen is well tolerated but associated with expected complications of hyperleukocytosis and DS, which require careful management. Our data supports the protocol recommendation for inpatient hospitalization to closely monitor patients during the first 2 weeks of induction.

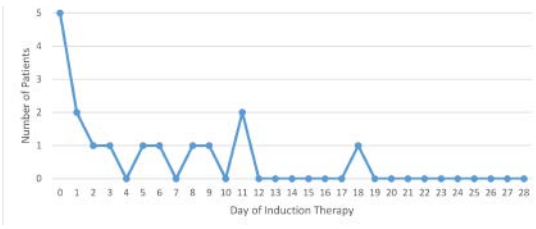

Figure 1. Incidence of differentiation syndrome by day indiction.

CO021
OUTCOME OF ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS EXPERIENCE OF CHILDREN WELFARE TEACHING HOSPITAL (2010-2015)

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Abstract. Acute promyelocytic leukemia (APL) is a rare subtype of childhood acute myeloid leukemia (AML). Although APL is now the most curable type of acute leukemia, this progress has not yielded equivalent benefit in developing countries. Bleeding complications

occur in 80% of patients at diagnosis and contribute to a higher incidence of early death in APL compared to other AML subtypes.

Aim of study. To report the clinical characteristics, early induction deaths and outcome of patients with APL treated in an oncology unit/ Children Welfare Teaching Hospital in Bagdad.

Patient and methods. From Jan. 2010- Dec.2015, a total of 181 consecutive patients with AML were admitted to the Oncology Unit, CWTH, Medical City-Baghdad. Of these, 46 (25.4%) cases were morphologically diagnosed as APL. The regimen used was an APL-specific protocol including ATRA + anthracycline combination.

Results. Within the study period, 46 patients were diagnosed with APL based on morphology. Ten patients were studied by molecular analysis and tested positive for the presence of PML-RARA transcript. The male to female ratio was 0.8:1. The median age was 9.1 years (range 9 months-14.2 years). Forty-four (92%) patients presented with pallor accompanied by a bleeding tendency in 36 cases (75%). There were 18 (39.1%) patients having WBC $\geq 10\times10^9$/L. Microgranular M3 variant was reported in 15 (32.6%) patients, of which 11 (73.3%) patients had WBC $\geq 10\times10^9$/L. Very early deaths were recorded in 9 (19.6%) patients, of which 7(15.2%) patients had fatal CNS bleeding and 2(4.4%) had a differentiation syndrome. With a median observation period of 31.3 months, range 2 days-80 months, event-free survival (EFS) for the treated group was 61% while overall survival was 63.4%. EFS of low-risk patients (70.4%) was significantly better than that of high-risk patients (42.9%) with a P value of 0.04. EFS of children treated with ATRA within the first 24 hours from hospital admission was higher than those who received it later, 72% and 43.8%, respectively with a P value of 0.06.

Conclusions and recommendations. Still, AML-M3 prevalence is high in Iraq and the 7-day mortality remains high. This study showed the significant difference in survival related to timing of starting ATRA. Event-free survival in our series was still below the standard, due to relatively high early mortality and relapse rate. This study highlights the need for better supportive care of children with APL, including early ATRA administration and aggressive transfusions and maintenance of higher platelet transfusion thresholds. In addition, early awareness of differentiation syndrome can have a significant impact to reduce the very early mortality rate.

CO022
ORAL ARSENIC AND RETINOIC ACID FOR CHILDREN WITH LOW-RISK ACUTE PROMYELOCYTIC LEUKEMIA

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Objective. Acute promyelocytic leukemia (APL) has now become a highly curable disease with the all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) as first-line treatment. Adult low-risk APL patients (WBC< 10 10^9/L) can be cured using only ATRA and ATO without chemotherapy. We also provided similar results using a totally oral (oral arsenic and ATRA), chemo-free outpatient protocol (Beijing protocol) for adult patients with low-risk APL. However, experiences in children with APL are scarce. These prompted us to try to extend the Beijing protocol to children patients with low-risk APL.

Methods. We conducted a single-centre pilot study to evaluate the efficacy of oral arsenic and ATRA for children patients with low-risk APL from April 2014 through October 2016. Nine patients with the median age of 16 years old (range 13-18) were enrolled and received oral arsenic realgar-indigo naturalis formula (RIF, 60 mg/kg) and ATRA (25 mg/m^2) as induction therapy until hematologic complete remission (CR). Hydroxyurea and/or cytarabine (without anthracyclines) were used to diminish the increased WBC during induction treatment. The post-remission therapy included RIF in a 4-week on and 4-week off, and ATRA in a 2-week on and 2-week off schedule for 7 months. The primary endpoint was the complete molecular response (CMR) post-consolidation, defined as absence of detectable PML-RARA transcripts by quantitative PCR. Secondary endpoints included CR, safety, hospital stay. Median follow-up was 15 months (range 6-36 months) by April 2017.

Results. All 9 patients achieved hematologic CR after a median time of 30 days. CMR rate was 100% at 3 and 6 months. Grade1,2,3, and 4 liver adverse events was 2,3,1,0, respectively. Differentiation syndrome occurred in 3 patients during induction. No hematological relapse or molecular relapse occurred at the last follow-up. Both the 2-year estimated EFS and OS were 100%. The total hospital time was 17 days (4-37 days) during the treatment phase. Of note, 100% (9/9) of patients completed the post-remission therapy on an outpatient basis without hospitalization. Patients resumed their usual lifestyle during post-remission therapy and their QoL was nearly normal during post-remission therapy.

Conclusions. Our study, which employed a largely home-based treatment protocol with complete oral regimen, chemo-free during induction in children patients with low-risk APL, proved to be effective, convenient.

CO023

ARSENIC TRIOXIDE CONSOLIDATION RESULTS IN EXCELLENT SURVIVAL IN YOUNG CHILDREN AS WELL AS OLDER CHILDREN AND ADOLESCENTS WITH NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP STUDY AAML0631

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Acute promyelocytic leukemia (APL) has become one of the most curable forms of myeloid leukemia because of the availability of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). ATO has proven very effective in relapsed APL and in decreasing relapses in adult patients with newly diagnosed APL. Studies by the European APL Group (APL 93 and APL 2000) suggested that young children <5 years old had high relapse risk (Bally et al, JCO, 2012). Thus, these young children with APL might particularly benefit from ATO therapy. Previously, data were limited on the efficacy of ATO in children with newly diagnosed APL, but the Children's Oncology Group (COG) performed a non-randomized phase III cooperative group trial (AAML0631) to evaluate the addition of 2 cycles of ATO to chemotherapy with reduced anthracycline. Here we report that this regimen resulted in excellent survival and low relapse rates across all pediatric age groups and especially the young children.

In COG AAML0631, risk group was determined by diagnostic white blood cell (WBC) count: standard risk (SR) WBC<10,000/μL and high risk (HR) WBC≥10,000/μL. Eligibility criteria were age 2-21.99 years, diagnosis of de novo APL, and PCR-confirmed PML-RARA. ATRA was given at 12.5 mg/m^2/dose PO BID on days 1-30 of induction and days 1-14 of each consolidation course and maintenance cycle. In addition to ATRA, chemotherapy included: Induction- idarubicin (IDA) 12 mg/m^2 3 doses; Consolidation 1- ATO 0.15 mg/kg IV daily 5 days/week 5 weeks repeated 2 cycles; Consolidation 2- cytarabine (ARAC) 1000 mg/m^2 IV q12h 6 days 1-3, mitoxantrone 10 mg/m^2 IV 2 days 3-4; Consolidation 3- IDA 5 mg/m^2 IV 3 days 1, 3, 5; Consolidation 4 (HR only)- ARAC 1000 mg/m^2 IV q12h 6 doses days 1-3, IDA 10 mg/m^2 IV once on day 4. Nine cycles of maintenance x12 weeks each included mercaptopurine 50 mg/m^2 PO daily and methotrexate 25 mg/m^2 PO once weekly. Intrathecal ARAC (age-based dosing) was given 4 times for SR and 5 times for HR APL including once each for consolidation 2-4 and cycle 1 maintenance.

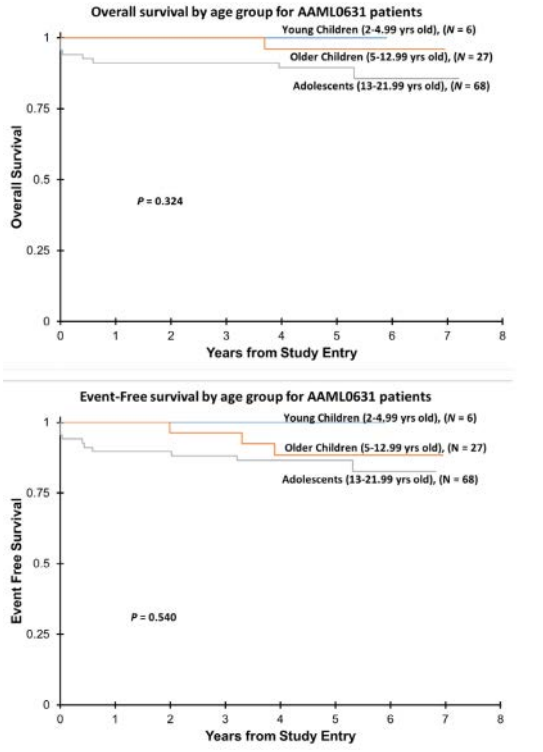

Figure 1.

Patients were enrolled from March 2009 to November 2012. There were 101 evaluable patients: young children age 2-4.99 years (N=6), older children age 5-12.99 years (N=27) and adolescents/young adults age 13-21.99 years (N=68). The HR group comprised 67% of young children, 22% of older children and 37% of adolescents (P=0.096). In 83% of young children, t(15;17) was the only cytogenetic abnormality, compared to 42% for older children and 70% for adolescents (P=0.028), suggesting that additional cytogenetic abnormalities are relatively uncommon in young children. Survival for all patients was excellent with 3-year OS 94 ±5%, EFS 91 ±6% and RR 3 ±4%. There were no differences in survival across the age groups: 3-year OS was 100%, 100% and 91 ±7% (P=0.32), EFS was 100%, 96 ±7% and 88 ±8% (P=0.54), and RR 0%, 4 ±8% and 3 ±5% (P=0.89), for young children, older children and adolescents, respectively (Figure 1). Our study is limited by the small number (N=6) of young children. However, APL is rare in this age group, and our findings provide useful information about the efficacy of ATO in this population. The AAML0631 regimen including ATO consolidation resulted in excellent survival and very low relapse risk in pediatric APL patients, including young children. This supports the inclusion of ATO in frontline therapy for pediatric APL.

CO024
ARSENIC TRIOXIDE (ATO) AND ATRA WITH LIMITED CHEMOTHERAPY (CT) IN NEWLY DIAGNOSED STANDARD RISK APL IN THE ELDERLY. A REPORT BY THE FRENCH BELGIAN SWISS APL GROUP (APL 2006 TRIAL)

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Background. Treatment of APL in the elderly with conventional ATRA-anthracycline based CT regimens is associated, like in younger patients, with very few relapses, but high death rates. Recent results have shown that, in standard risk APL, ATRA+ATO combinations (without CT) are at least as effective as classical ATRA + CT regimens while being less myelosuppressive (Lo Coco 2014; Burnett 2015) thus constituting a very appealing approach for elderly patients. However, when our APL 2006 trial started, the feasibility of treatment of APL without CT was unknown. Furthermore, access to ATO still remains limited for frontline treatment of APL in most countries. We present results of APL 2006 trial, where we combined ATO to ATRA and reduced CT in patients aged older than 70 with standard risk APL.

Methods. Between 2006 and 2015, newly diagnosed APL patients (pts)>70 years with WBC <10 G/L received induction treatment with ATRA 45 mg/m^2/d until CR and Idarubicin (Ida) 9 mg/m^2/d on days 3, 5 and 7, a first consolidation course with Ida 9 mg/m^2/dx3 combined with ATO 0.1 mg/kg/d during 25 days, a second consolidation course with ATO (same schedule) and ATRA during 15 days, followed by maintenance during 2 years with intermittent ATRA continuous 6 MP+MTX, plus 15 days ATO cycles every 3 months during the first maintenance year. In Sept 2010, after inclusion of 55 patients, because mortality in CR was still high (10/51 CR pts) while no relapse was observed, consolidation CT was reduced to one day of Ida during the first consolidation cycle. The primary endpoint was event-free survival (EFS) from CR achievement. We present here results at the reference date of Jan, 1, 2016. Results. Median age of the 123 pts included (after excluding one diagnosis error) was 73.6 years (range 70-88.4), with 56 % males. 113 (92%) pts achieved CR, 4 (3%) had resistant leukemia, and 6 (5%) had early death from sepsis (n=3), and multiorgan failure (n=3). Of the 113 CR pts, 3 relapsed (5-year cumulative incidence of relapse of 2.9%), with no significant difference across periods (p=0.10, Gray's test). 14 (12%) patients died in CR, including 4/62 (4%) accrued after vs 10/51 (20%) before the amendment (p=0.045, Fisher's test). Causes of death in CR were sepsis (n=4 before and 2 after amendment), bleeding (n=5 before and 1 after), general deterioration (n=1 before) and prostate cancer (n=1 after). 5-year OS was 80% (95%CI, 73-88%) and 5-year EFS was 80% (95%CI, 73-88%), with no difference according to period (p=0.71 and p=0.80 by the log-rank test, respectively). Mean time to ANC>1 G/L and platelets> 50G/l after the first consolidation course was 16.2 and 11.9 days in the original vs 5.6 and 4.0 days in the amended protocol (p<0.0001 and p<0.0001), while the second consolidation course was not associated with myelosuppression.

Conclusions. In this very old patient population (>70 years) with standard risk APL, addition of ATO, that allowed reduction of the amount of CT administered, was associated with high CR rates, without any increase (and a possible reduction) in the relapse rate compared to our previous experience with ATRA-CT regimens. However, reduction of mortality in CR with this regimen was only seen when consolidation CT was reduced to one single day of Ida. This is further evidence of the role of ATO in a patient population in whom myelosuppression must be avoided.

CO025
COMPARING ARSENIC TRIOXIDE AND INDIGO NATURALIS FORMULA IN PEDIATRIC PATIENTS WITH ACUTE PROMYELOID LEUKEMIA: AN INTERIM REPORT OF MUTICENTER AND RANDOMIZED CLINICAL TRIAL SCCLG-APL

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Background. Indigo naturalis formula (RIF) is a traditional Chinese medicine with tetraarsenic tetrasulfide, indirubin and tanshinone IIA as major active ingredients. RIF can be taken orally, which reduces hospital days. Event-free survival (EFS) is about 90% in adult patients with acute promyelocytic leukemia (APL) treated on protocol containing RIF, all-trans retinoic acid (ATRA) and chemotherapeutic agents (RIF+ATRA+chemotherapy), which is comparable to that of patients on arsenic trioxide (ATO)+ATRA+chemotherapy. However, the efficacy and safety of RIF in pediatric counterpart have not been evaluated, and it is unclear whether RIF can replace ATO.

Methods. SCCG (South China Children Leukemia Group)-APL protocol was started in august 2011. Patients of age 0-16 were enrolled except those having intracranial hemorrhage / central nervous system leukemia with coma, convulsion or nervous paralysis at diagnosis. Patients were randomized into ATO or RIF group and received "ATO/RIF+ATRA+low-dose anthracycline" for induction and consolidation therapy followed by "ATO/RIF+ATRA+MTX+6MP" for 96 weeks of maintenance therapy. Those with high-risk APL (WBC ≥ 10^9/L at diagnosis) received additional Ara-C in consolidation phase.

Results. Among 84 patients diagnosed, 78 met the enrollment criteria and were willing to be randomized. Headache and vomit/nausea were the commonest treatment-related adverse effects occurring in 18% and 12% of patients in each group during induction and consolidation therapy respectively. Significant treatment-related infections including sepsis, pneumonia, cellulitis and etc. were observed in 13% and 8% of patients during induction, and 12% and 8% of patients during consolidation, in ATO and RIF groups, respectively (p>0.05). There were two drop-out cases in ATO group, one abounded treatment and the other deviated from the protocol because of adverse effect. The 4-year EFSs (median follow-up of 2 years) of both groups were 100%.

Conclusions. SCCG-APL protocol containing arsenic (either ATO or RIF), ATRA and low-intensive chemotherapy obtained a good outcome in childhood APL including high-risk.

ClinicalTrials.gov ID: NCT02200978

CO026
COMPARISON OF INDUCTION THERAPY IN ACUTE PROMYELOCYTIC LEUKEMIA WITH ARSENIC TRIOXIDE ALONE OR IN COMBINATION WITH ATRA

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Background. Acute promyelocytic leukemia (APL) is a curable sub type of acute myeloid leukemia which in recent years using new therapy strategies such as combination therapy leads to improved outcomes. A randomized clinical trial study conducted and the outcome of patients who treated with arsenic trioxide (ATO) alone compared with patients who treated with combination of ATO and ATRA.

Patients and methods. Totally 67 APL patients enrolled from 2012 to 2016 and all patients with WBC ≤ 10,000 were randomly allocated into two groups. First group with 30 patients with a median age of 29 years (range 13-70) received ATO and in second group with 37 patients with a median age of 37 years (range 14-60) received ATO plus ATRA (p=0.23). ATO infused 0.15 mg/kg/day till achieve complete remission for maximum 60 days and after 28 days rest, again begin ATO for 28 days as consolidation four times separated by 28 days rest. In group of patients who randomize to ATO+ATRA add 45 mg/m^2/day ATRA to ATO protocol. All patients followed up for survival, relapse and treatment related complications.

Results. All patients except one patient in ATO group were alive after median 18 and 17 months of follow-up in two groups respectively and 2.5 year overall survival in ATO group was 86% (p=0.32). Five patients encountered relapse in ATO group and 2.5 year leukemia free survival was 60% in this group but no relapse occurred in ATO plus ATRA group (p=0.01). The median of WBC at diagnosis were 1,840 and 1,800 in ATO and ATO plus ATRA group respectively (p=0.67). The median of platelets at diagnosis were 25,000 and 27,000 in ATO and ATO plus ATRA group respectively (p=0.15). Liver dysfunction occurred in 24 patients of ATO group and in 25 patients of ATO plus ATRA group (p=0.37). Renal test impairment occurred in 9 and 11 patients in ATO and ATO plus ATRA group respectively (p=0.95).

Conclusions. New treatment strategies for APL improved outcomes of disease. However, according recent studies, ATO has been considered as first line therapy in APL patients but several studies showed improvement of outcome with combination therapy added to ATO. This study showed significant decrease in relapse with combination of ATO and ATRA in APL patients. The long follow-up of patients might be reveal more accurate result of combination therapy.

Keywords. Acute promyelocytic leukemia, Arsenic trioxide, ATRA, Combination therapy

CO027
FRONTLINE THERAPY OF ACUTE PROMYELOCYTIC LEUKEMIA: RANDOMIZED COMPARISON OF ATRA AND INTENSIFIED CHEMOTHERAPY INCLUDING HIGH DOSE CYTOSINE-ARABINOSIDE VERSUS ATRA AND ANTHRACYCLINES - A PROSPECTIVE MULTICENTER RANDOMIZED CLINICAL TRIAL

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Eighty-seven patients with genetically confirmed acute promyelocytic leukemia (APL) of all Sanz risk groups were randomized to uniform therapy with all-trans retinoic acid (ATRA) and intensified double induction including high dose cytosine arabinoside (HD ara-C) (German AMLCG) or to risk adapted therapy with ATRA and anthracyclines (Spanish PETHEMA, LPA99). Median age of the 80 eligible patients was 52 years (y) (20 to 87). The outcome (median follow up 5.9 y) was similar in both arms. AMLCG vs PETHEMA: hematological complete

remission (CR) 87% vs 83%, early death 13% vs 17% (p=0.76). Overall, event-free, leukemia-free survival, cumulative incidence of relapse at 6 y was 75% vs 78% (p=0.92); 75% vs 68% (p=0.29); 86% *v*s 81% (p=0.28); 0% vs 12% (p=0.04, no relapse vs four relapses), respectively. The AMLCG regimen was associated with a significantly longer duration of peripheral neutropenia (p=0.02) and a higher rate of WHO grade ≥ 3 infections. By time-to-event analysis, the median time (from the start of induction until end of consolidation therapy) to achieve the RT-PCR conversion (PML-RARA) from 'PCR-positive to negative' was 60 days in both arms (AMLCG 95%CI 49-78 days; PETHEMA 95%CI 45-91 days) (p=0.12).

Follow up data showed five deaths in CR, three in the AMLCG arm (all due to secondary malignancy) and two in the PETHEMA arm (caused by secondary malignancy or liver cirrhosis), respectively. In eight patients (12% of patients who entered CR), a secondary malignancy was observed leading to death in CR of APL in four patients 3.2 to 5.6 years after start of APL therapy (n=4 in the AMLCG arm: MDS/AML, n=2; pancreatic cancer, n=1; prostate cancer, n=1 (n=4 in the PETHEMA arm: MDS/AML, n=3; chondrosarcoma, n=1), respectively. All four relapses were successfully salvaged with arsenic trioxide (ATO) plus ATRA followed by autologous (n=1) or allogeneic transplantation (n=2) or further ATO (n=1) and are in ongoing CR at 3.0 to 7.2 years after first relapse.

Conclusions. The small number of patients limits the reliability of conclusions. With these restrictions, the outcomes of both approaches were similar and show the limitations of ATRA and chemotherapy. The HD ara-C containing regimen was associated with a lower relapse rate in high risk APL.

CO028
LONG-TERM OUTCOME OF PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH ALL-TRANS-RETINOIC ACID, ARSENIC TRIOXIDE, AND GEMTUZUMAB OZOGAMICIN

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The combination of all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) has been shown to be superior to ATRA plus chemotherapy in the treatment of standard risk newly diagnosed patients with acute promyelocytic leukemia (APL). A recent study demonstrated the efficacy of this regimen with added gemtuzumab ozogamycin (GO) in high-risk patients. We examined the long-term outcome of newly diagnosed APL patients treated at our institution on three consecutive prospective clinical trials using the combination of ATRA, ATO, with or without GO. For induction all patients received ATRA (45 mg/m^2 daily) and ATO (0.15 mg/kg daily) with a dose of GO (9 mg/m^2 on day 1) added to high risk patients (WBC > 10×10^9/L), as well as low risk patients who experienced leukocytosis during induction. Once in complete remission (CR), patients received 4 cycles of ATRA plus ATO consolidation. 187 patients, including 54 with high risk and 133 with low risk disease have been treated. The complete remission rate was 96% (52 of 54 in high risk, 127 of 133 in low risk). Induction mortality was 4% with only 7 relapses. Among low risk patients, 60 patients (45%) required either GO or idarubicin for leukocytosis. Median duration of follow-up was 47.6 months. The five-year event-free, disease-free, and overall survival rates are 85%, 96%, and 88%, respectively. Late hematological relapses beyond 1 year occurred in 3 patients. Fourteen deaths occurred beyond 1 year; 12 were related to other causes. This study confirms the durability of responses with this regimen.

CO029
ORAL ARSENIC AND RETINOIC ACID FOR HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA

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Objective. Acute promyelocytic leukemia (APL) has now become a highly curable disease with the all-trans retinoic acid (ATRA) and arsenic trioxide (ATO)-based treatment. The practice-changing study APL0406 reported by Lo Coco *et al* demonstrated that non-high-risk APL patients (WBC< 10×10^9/L) can be cured using only ATRA and ATO without chemotherapy.We also provided similar results using a totally oral (oral arsenic and ATRA), chemo-free outpatient protocol (Beijing protocol) for non-high-risk APL patients. 3 For high-risk patients (WBC≥ 10×10^9/L), attempts at minimizing chemotherapy have proven feasible with the use of gemtuzumab ozogamicin (GO)+ATRA +ATO, a combination allowing to achieve an overall survival (OS) of 65%-87%.4,5 Because of the lack of availability of GO outside of Europe, ATO infusing in hospital settings and a relative inferior outcomes, a novel optimal regiment is yet to be determined. These prompted us to try to extend the Beijing protocol to high-risk patients.

Methods. From April 2014 through September 2016 we conducted a single-centre pilot study to evaluate the efficacy of oral arsenic and ATRA for high-risk APL patients. Twenty patients were enrolled and received oral arsenic realgar-indigo naturalis formula (RIF, 60 mg/kg)

and ATRA (25 mg/m^2) as induction therapy until hematologic complete remission (CR). Hydroxyurea and/or cytarabine (without anthracyclines) were used to diminish the burden of leukemia during induction treatment. The post-remission therapy included RIF in a 4-week on and 4-week off , and ATRA in a 2-week on and 2-week off schedule for 7 months. The primary endpoint was the complete molecular response (CMR) post-consolidation, defined as absence of detectable PML-RARA transcripts by quantitative PCR. Secondary endpoints included CR, safety, hospital stay, medical costs, and the quality of life (QoL) measured by FACT-G. Median follow-up was 23 months (range 6-35 months) by March 2017.

Results. The median age of the all patients was 35.5 (16-61 ys) years old. All 20 patients achieved hematologic CR after a median time of 30 days(28-55 days). CMR rate was 85% and 100% at 3 and 6 months. Grade 3-4 liver adverse events and differentiation syndrome occurred in 0 and 7 patients during induction. Only one patient had molecular relapse at 15 months and achieved second CMR after one further cycle of treatment with ATRA and RIF. No hematological relapse occurred at the last follow-up. The 3-year estimated EFS and OS were 99.0% (95% CI, 63.2%-99.0%) and 100%. The total hospital time was 25 days (4-37 days) during the treatment phase. Of note, 100% (20/20) of patients completed the post-remission therapy on an outpatient basis without hospitalization. Patients resumed their usual lifestyle during post-remission therapy and their QoL was nearly normal during post-remission therapy.

Conclusions. Our study, which employed a largely home-based treatment protocol with complete oral regimen, chemo-free except for only minimal cytoreductive chemotherapy during induction in high-risk APL, proved to be effective and convenient. This approach exemplifies an ideal model for the treatment of high-risk APL. However, strict clinical and laboratory monitoring of these patients for long-term outcome are warranted.

CO030
CLINICAL SIGNIFICANCE OF CD56 EXPRESSION IN PATIENTS WITH DE NOVO ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH THE PETHEMA LPA96, LPA99 AND LPA2005 PROTOCOLS: AN UPDATED ANALYSIS

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Background. A higher relapse rate has been reported among acute promyelocytic leukemia (APL) patients with CD56 expression in leukemic blasts at diagnosis. This prognostic impact was demonstrated among patients treated with chemotherapy plus ATRA based protocols (e.g, 651 patients included in PETHEMA trials), being an independent risk factor.

Objectives. In this study we confirm the impact of CD56 expression in a larger series of patients with non-secondary genetically confirmed de novo APL, homogeneously treated with three consecutive multicenter PETHEMA trials.

Materials and methods. Between 1996 and 2012, 1559 consecutive adult and pediatric patients were enrolled in the PETHEMA LPA 96, 99 and 2005 trials from the PETHEMA, HOVON, GATLA, and PALG groups. CD56 expression was analyzed on bone marrow samples at diagnosis in local laboratories, and was available on 940 patients (60%). Treatment consisted of Induction therapy with oral ATRA (45 mg/m^2/d) and intravenous idarubicin (12 mg/m^2/d x4 days) followed by three courses of consolidation with anthracycline monochemotherapy. In the PETHEMA 99 trial ATRA was added in each cycle of consolidation for intermediate and high risk patients, according to Relapse-risk score. Ara-C was added in consolidation for high-risk patients in the LPA2005 trial. In all trials, maintenance therapy consisted of intermittent ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurine.

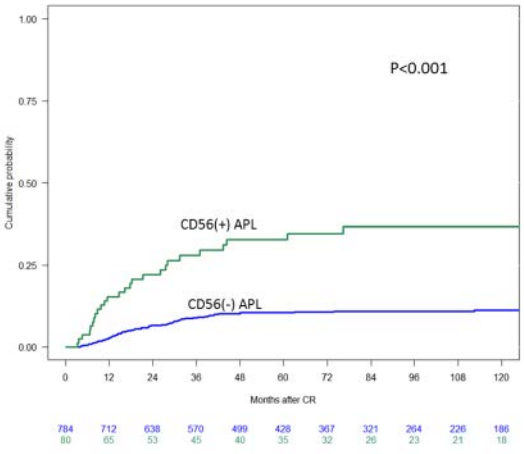

Figure 1. CIR in CD56+ patients and CD56-.

Results. Overall, 90 patients (10%) had CD56 positive APL (*i.e*, ≥20% of leukemic blasts CD56+). CD56(+) APL was significantly associated with high white blood cell counts; low albumin levels; worse ECOG; BCR3 isoform; and the coexpression of CD2, CD34, CD7, HLA-DR, CD15, and CD117 antigens. There was a higher induction death rate in patients with CD56+ APL (16% *vs* 8%, respectively, p=0.02). For CD56(+) APL, the 5-year cumulative incidence of relapse was 33%, compared with a 10% rate for CD56(-) (p=0.006). The CIR at 5 years was higher among CD56+ APL irrespectively of the Sanz score (low-risk 47% vs 5%, p<0.001; intermediate 23% vs 7%, <0.001; and high-risk 42% vs 21%, p=0.007). In the multivariate analysis, CD56 expression retained the statistical significance (p<0.0001), together with higher relapse-risk score

(p=0.001), and male gender (p=0.05). CD56(+) APL also showed a greater risk of CNS relapse (6% vs 1%, p<0.001). For CD56(+) APL, the 5-year overall survival was 75%, compared with a 83% in CD56(-) APL (p =0.03). In summary, this study confirms the relevance of CD56 expression as an independent adverse prognostic factor for relapse in patients with APL treated with all-trans-retinoic acid plus idarubicin-derived regimens. This marker was incorporated in the ongoing AIDA-based LPA2012 trial for implementing risk-adapted consolidation in APL.

CO031
CHARACTERISTICS AND CLINICAL OUTCOME OF PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA AND INCREASED BODY MASS INDEX TREATED WITH THE PETHEMA PROTOCOLS

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Background. It has been suggested that increased body mass index (BMI) correlates with development of differentiation syndrome (DS), as well as an increased cumulative incidence of relapse (CIR) in patients with newly diagnosed acute promyelocytic leukemia (APL). However, no large studies have confirmed the prognostic value of BMI in APL patients treated with All-trans retinoic acid and chemotherapy based protocols.

Objectives. In this study we aim to analyze the impact of BMI on disease characteristics and clinical outcome of a large series of patients with genetically confirmed de novo APL, homogeneously treated with three consecutive multicenter PETHEMA trials.

Material sand methods. Between 1996 and 2012, 1419 consecutive adult patients were enrolled in the PETHEMA LPA 96, LPA 99, and LPA2005 trials. Treatment consisted of Induction therapy with oral ATRA (45 mg/m^2/d) and intravenous idarubicin (12 mg/m^2/d x4 days) followed by three courses of consolidation with anthracycline monochemotherapy. In the PETHEMA 99 trial ATRA was added in each cycle of consolidation for intermediate and high risk patients, according to Sanz score, while in the LPA2005 cytarabine was added in consolidation for high-risk. Maintenance therapy consisted of intermittent ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurine.

Results. Overall, 1320 adult patients (93%) had available data on baseline weight and the BMI was calculated. Of them 545 (41%) had under/normal weight (BMI <25) and 775 (59%) were overweight/obese (BMI ≥25). An increased BMI was associated with older age (mean 48 vs 38 years old, p< 0.0001), increased mean serum levels of urea, creatinine, uric acid, triglycerides, cholesterol (all p<0.0001), bilirubin (p=0.002), and male sex (p<0.0001). Overweight/obese patients showed a trend towards more thrombosis during induction (p=0.06), and higher induction mortality (p=0.05). No relation was observed between BMI and development of DS (27% in in both overweight/obese and under/normal weight). The estimated CIR at 5 years was 12.6% in overweight/obese and 12.6% in underweight/normal weight patients (p=0.69). The estimated OS and EFS at 5 years was 80.2% and 73.7% in overweight/obese and 84.2% and 78.0% in underweight/normal weight patients (p=0.006 and p=0.02, respectively). Multivariable analysis showed that a BMI ≥25 was not an independent predictor of OS (p=0.48), contrarily to older age, higher relapse-risk (both p<0.0001), and LPA96&99 trials (p=0.001).

Conclusions. The prognostic impact of BMI was not confirmed in this large series of adult APL patients homogeneously treated with ATRA and chemotherapy. We were able to confirm the previously reported relationship between increased BMI, male gender, and older age, as well as other well known laboratory abnormalities of obese patients.

CO032
PROLONGED ATO AND ATRA THERAPY FOR RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA

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Background. Salvage therapy for APL patients who relapse after ATRA and chemotherapy is based on Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA). However, after the achievement of a second remission, the best consolidation approach including or not an SCT procedure remains controversial. The role of a prolonged ATRA-ATO approach with repeated cycles has not been investigated in the APL relapse setting. We report herein a retrospective analysis of 22 relapsed APL patients treated with prolonged ATO-ATRA therapy at two Italian institutions.

Patients and methods. Twenty-two adult patients with APL in first (17 patients) or second (5 patients) relapse treated between 2006-2017 in 2 Italian Hematology Institutions (Policlinico Tor Vergata and Policlinico Umberto I, Rome) were included in this study. All patients received ATO-ATRA as reported elsewhere (Lo Coco, NEJM 2013) for induction and consolidation followed or not by transplant procedures. Molecular analysis of PML/RARA was carried out after the second ATRA-ATO cycle, at the end of therapy and at different time points during follow-up.

Results. Median age was 43.5 (range:18-80 yrs). At the time of relapse, 7 patients had hematologic disease recurrence, 14 molecular relapse (1 in association with leukemia cutis and 2 with CNS disease) and 1 isolated extra-

medullary relapse. All patients had been treated with the AIDA regimen (ATRA and standard chemotherapy) front-line and the median length of the pre-ATRA-ATO CR was 32.5 months (range: 5-120) with 18 patients in CR1 for ≥ 12 months. As salvage therapy, ATO-ATRA was administered for 5 cycles (14 patients), 4 cycles (4 patients), 3 cycles (2 patients), 2 cycles (1 patient) and was early discontinued after induction in 1 case due to progressive disease. Nineteen of 22 patients (87%) obtained molecular remission already after the 2nd ATO-ATRA cycle, while 3 patients showed disease progression during treatment. One patient underwent allo-HSCT from an HLA-identical donor and one received auto-HSCT, while the remaining received only ATO-ATRA due to their long previous remission (7 patients), because of advanced age and/or unfitness for intensive chemotherapy (5 patients), refusal of HSCT procedure (3 patients), lack of a donor (2 patients) or medical decision (2 patients). At a median follow-up of 58 months from the time of relapse (range: 21-128), 14/22 pts (63.6%) are alive and in CRm and 1 died of unrelated causes while in CRm; of these, 1 patient only underwent auto-SCT after ATO-ATRA therapy. Finally, 4/22 patients relapsed at a median of 15 months and 3/22 patients showed progressive disease; of these 4/22 (18%) died while 3/22 (13%) are still alive and in CRm after subsequent salvage regimens.

Conclusions. Although based on a retrospective series, this study suggests a potentially curative effect of the prolonged ATRA-ATO regimen used as salvage therapy for APL patients relapsed after a long CR1 achieved with front-line ATRA and chemotherapy. Prospective studies are warranted to confirm these observations.

CO033
CHARACTERISTICS AND OUTCOME OF PATIENTS WITH THERAPY-RELATED ACUTE PROMYELOCYTIC LEUKEMIA FRONT-LINE TREATED WITH OR WITHOUT ARSENIC TRIOXIDE-AN INTERNATIONAL COLLABORATION STUDY

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Background. Reports of patients (pts) with therapy-related acute promyelocytic leukemia (t-APL) have increased in recent years (yrs) and retrospective studies have suggested that their outcomes were similar to those of pts with de novo APL. More recently, arsenic trioxide (ATO)/all-trans retinoic acid (ATRA) has been shown to be the most effective therapy in de novo APL with low/intermediate Sanz score (Lo Coco F. *et al*. NEJM, 2013). So far, this regimen has not been evaluated systematically in t-APL pts. Aims: To describe outcome in a large series of t-APL pts and to compare outcomes after treatment with ATO/ATRA with that after chemotherapy (CTX)/ATRA. Methods: We retrospectively studied 103 t-APL pts (median age, 59 yrs; range, 18-80 yrs), treated between 1991 and 2015 within 11 study groups/institutions of the US and Europe. Pts had received i) CTX/ATRA (n=53; either daunorubicin/ idarubicin+ ATRA for induction and different CTXs+ATRA for consolidation), ii) ATO/ATRA (n=24; according to Lo Coco F. *et al*. NEJM, 2013 (n=21) or Burnett AK, *et al*. Lancet Oncol, 2015 (n=3)), iii) CTX/ATO/ATRA (n=19; according to Gore SD, *et al*. JCO, 2010), and ATRA alone (n=7).

Results. In 87/103 t-APL pts, a solid cancer was the primary malignancy, most commonly breast (n=38) and pro-

state (n=14) cancers. A prior hematologic neoplasm (non-Hodgkin lymphoma, n=5; Hodgkin lymphoma, n=3) or autoimmune/rheumatological disease was present in 8 pts, each. Median latency between primary malignancy/disease and occurrence of t-APL was 3.5 yrs (range, 0.4-26.2 yrs). In univariable analysis, prior treatment with neither intercalating agents (p=0.81) nor topo-II inhibitors (p=0.46) was associated with the length of the latency period between diagnosis of primary malignancy and the occurrence of t-APL. Risk categorization based on WBC at diagnosis was low/intermediate-risk (WBC <10.0 G/l) in 80 (81%) pts. Baseline characteristics of the treatment groups were comparable except than ATRA pts were significantly older (p=0.002) and had lower platelet counts (0.009). Complete remissions were achieved after induction therapy in 57% with ATRA, 100% with ATO/ATRA, 78% with CTX/ATRA, and 95% with CTX/ATO/ATRA. Early death rates were 43% for ATRA, 0% for ATO/ATRA, 12% for CTX/ATRA, and 5% for CTX/ATO/ATRA. Three pts relapsed, two developed therapy-related acute myeloid leukemia (all 5 pts after CTX/ATRA treatment) and 13 died in remission including seven pts with recurrence of the prior malignancy. Median follow-up for survival was 3.7 years. None of the pts treated with ATRA alone survived beyond one year. Event-free survival was significantly higher after ATO-based therapy (95%, 95%-CI, 82-99%) as compared to CTX/ATRA (78%, 95%-CI, 64-87%; p=0.042), if deaths due to recurrence of the prior malignancy were censored. The estimated 2-year overall survival in intensively treated pts was 88% (95%-CI, 80-93%) without difference according to treatment (p=0.47). Febrile neutropenia of grade ≥3 during induction therapy was less frequent in pts treated with ATO/ATRA as compared to CTX/ATRA or CTX/ATO/ATRA (p=0.03), whereas the occurrence of other grade ≥3 toxicities was not different between treatment groups.

Conclusions. The ATO-based regimen for first line treatment of t-APL pts was associated with excellent and sustained response rates. These data demonstrate the important potential of ATO/ATRA in the primary management of t-APL pts.

CO034
MUTATIONAL ANALYSIS OF MDS AND AML OCCURRING AFTER TREATMENT FOR ACUTE PROMYELOCYTIC LEUKEMIA
A REPORT OF 9 CASES

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Background. 1-2% of APL treated with ATRA-chemotherapy (CT) develop MDS/AML (non APL), a problematic side effect for a highly curable disease. Characteristics of those MDS/AML (Del 5q/-7/del7q often complex) are those of alkylator type therapy-related (t-MDS/AML). In a report on NPM1 mutated AML that evolved to NPM1 negative MDS , we found that other somatic mutations present at the MDS phase were already present at AML diagnosis, suggesting an underlying MDS (with secondary acquisition of NPM1 mutation) (Morin,NEJM, 2016,11;375(6):e9). As APL secondary to MDS has also been reported, we wondered whether MDS/AML after APL were t-MDS/AML, or underlying MDS with APL progression.

Methods. Among 956 newly diagnosed APL treated with ATRA-CT (APL 2006 trial), 9(1%) developed MDS/AML (non APL) in first CR. Paired marrow samples at APL and MDS/AML diagnosis were analyzed on genomic DNA for the 30 most frequently mutated genes in MDS/AML, by NGS

Results. Median age of the 9 cases of MDS/AML was 52 years, and median interval from diagnosis of APL treatment to MDS/AML diagnosis was 2.8 years. No MDS morphological features were reported on APL diagnosis marrow aspirates. All the patients developed MDS/AML in first CR. Karyotype at APL diagnosis found no abnormalities in addition to t(15;17) in the 9 pts. Karyotype at MDS/AML diagnosis showed: -7/del7q (n=6), del(5q-)/-5 (n=5), del (17p) (n=2), and was complex in 5 cases. Mutations identified at APL diagnosis were FLT3-ITD mutations (n=4), FLT3-TKD mutations (n=2), mutations in WT1 (n=2), NRAS, PHF6, DNMT3A (1 case each). At MDS/AML diagnosis, 7 patients had detectable mutations, while the remaining 2 pts had a complex karyotype typical of t-MDS/AML (table). The most frequently mutated gene at MDS/AML diagnosis was TP53 (3/9 cases), while other mutations involving ASXL1, CBL, DNMT3A, EZH2, GATA2, KRAS, PTPN11, RUNX1, TET2 ,and SMC1A were seen in one patient each, and 5 pts had several mutations. None of the mutations identified at APL diagnosis was found at MDS/AML diagnosis, and vice versa, strongly suggesting that APL and MDS/AML arose from distinct clones.

Conclusions. No evidence of underlying MDS was found at APL diagnosis Cytogenetic and mutational profiles of those MDS/AML were suggestive of t-MDS/AML. Thus, MDS/AML occurring during the course of APL treated with ATRA and CT have characteristics of therapy-related cases.

CO035
THE REAL WORLD OF ARSENIC USES IN CHINESE WITH ACUTE PROMYELOCYTIC LEUKEMIA: A CROSS-SECTIONAL SURVEY

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Objective. Arsenic has become first-line treatment of acute promyelocytic leukemia (APL) since 2013 according to NCCN Guidelines Acute Myeloid Leukemia Version 2.2013, but little information is available about the real world of arsenic uses in China. We aimed to evaluate the usage of arsenic and assess the current status of the treatment of APL in China.

Methods. Noninterventional, cross-sectional survey using electronic questionnaires distributed to APL patients and answered anonymously.

Results. In total, 237 respondents were evaluable and 120 respondents (50.6%) were male. Median age was 40 years (range 15-68 years). Median time from diagnosis to this survey was 15 months. Valid submissions came from 28 of 34 provinces and municipalities. There were 77.64% respondents hospitalized within three days since diagnosis. The percentage of respondents received arsenic during induction treatment was 73.8% (175/237), including arsenic trioxide (ATO) (n=136) and oral arsenic (n=39). However, the percentage increased up to 100% (237/237) during the post-remission treatment phase, including ATO (n=137) and oral arsenic (n=100). Interestingly, 32.9% respondents considered the costs of ATO acceptable by themselves. However, 92.4% respondents regarded the burden of oral arsenic was high because it was not covered by health insurance, and 95.8% respondents appeal to oral arsenic covered by health insurance. The proportion of respondents covered by Basic Insurance for Urban Employees, Basic Insurance for Urban Residents, the New Rural Cooperative Medical Scheme and Commercial insurance were 3.8%, 44.3%, 38.4% and 5.9%. In total, 99.16% respondents hope to receive a chemotherapy-free outpatient treatment protocol.

Conclusions. High proportion of APL patients received arsenic as first-line treatment in China, which may result from the relative low price of arsenic. A chemotherapy-free outpatient treatment model worthy to explore.

CO036
AVAILABILITY OF ATRA, BLOOD BANK SUPPORT, TREATMENT PROTOCOLS AND HEMATOLOGISTS/ONCOLOGISTS FOR MANAGEMENT OF APL IN TWO STATES (MICHIGAN AND LOUSIANA) IN THE USA

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Introduction. Acute Promyelocytic Leukemia (APL) is a subtype of AML characterized by pancytopenia, and bleeding. The cause of bleeding is due to thrombocytopenia and disseminated intravascular coagulation. Excellent targeted drugs are available with cure rates >90% in clinical trials treated on a protocol. Given the nature of APL, ≈30% of patients in the general population die during induction, due to bleeding, differentiation syndrome (DS) and infection. Immediate transfusion support, ATRA initiation, and prevention of DS are key to decreasing early deaths. In the leukemia community, concerns exist about prompt availability of ATRA, blood bank support, treatment protocols, and trained physicians in community hospitals. We conducted a survey to collect data on these issues required for successful treatment of APL.

Methods. Using Surveillance, Epidemiology, and End Results (SEER) registry data, we identified the states of Michigan (MI) (population: 9.9 million) and Louisiana (LA) (population: 4.7million) due to their low one year APL survival rate. All eligible hospitals (253) were obtained from the Data Medicare online directory (https://data.medicare.gov/). Each hospital was contacted to exclude non-APL treatment centers. We contacted the remaining 23 APL treatment centers (9 LA; 14 MI) and conducted a telephone survey of 7 questions (Figure 1) with a pharmacy staff member, other hospital staff and hematologists.

Results. ATRA was available (on formulary and/or in stock) at 6of the 23 hospitals.4 of the 6 hospitals with ATRA were affiliated with a school of medicine (SOM).

7 hospitals answered a follow-up question about the lack of ATRA. Common answers were the pharmacist was unfamiliar with the drug (71%) or there had not been a recent request (29%).

For 17 hospitals that did not have ATRA, responses when asked about the viability of obtaining it, were:

1. Needs approval of P&TCommittee, 7/17
2. Could be available within one to two days, 3/17
3. Could be available within two weeks, 3/17
4. Could not give an exact timeline, 4/17

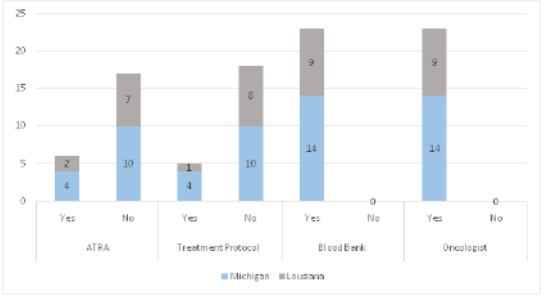

Figure 1.

Regarding availability of a written protocol, 5 of 23 hospitals stated they follow a protocol for treating APL. Of the 5 hospitals, only 1 was not affiliated with a SOM. Furthermore, of the 5 hospitals with a protocol,3 (2 SOMs) have their own written protocol and 2 (1 SOM)follow the National Comprehensive Cancer Network (NCCN) guidelines. For the 18 hospitals that

lacked a protocol nor followed the NCCN guidelines, an expedited and tailored approach was used based on patient's age, blood counts, and health issues.

All APL treating hospitals had staff hematologists and a blood bank with the capability to meet the transfusion requirements.

Conclusions. Despite the amount of literature about early deaths and early ATRA introduction to treat APL, many hospitals are unable to meet this demand due to lack of prompt availability of the drug. All APL treating hospitals had trained physicians and adequate blood bank support. Since most of the hospitals surveyed do not have a treatment protocol, we believe the outcome could be improved if a simplified set of treatment guidelines are developed for all hospitals treating APL.

CO037
RETROSPECTIVE ANALYSIS OF EARLY MORTALITY IN A COHORT OF PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia, with high cure rates using current treatments. APL typically presents with coagulation disorders and intracranial hemorrhage remains an important treatment failure event. Although early death rates of less than 10% are reported in clinical trial, this number is higher in real life non-selected patients.

Objective. Compare characteristics between patients who died and survived induction chemotherapy.

Methods. Data of newly diagnosed APL patients from January 2009 to February 2017 was retrieved from a tertiary academic hospital database. Available data from 63 patients was obtained.Sanz score was used to divide patients into risk groups. Treatment protocol in our institution consists of idarubicin plus tretinoin based treatment according to risk group, with prednisolone as prophylaxis for differentiation syndrome. Hydroxyurea is admitted for initial cytorreduction.

Results. In total, 63 patients were diagnosed, with a median follow-up of 66 months and 71% overall survival. Thirteen (21%) patients died before induction was completed, 8 from central nervous system (CNS) vascular events (5 hemorrhagic) and 5 from infection. All induction survivors achieved complete remission, 26% with molecular remission, and 4 deaths occurred afterwards, 2 from CNS events (1 hemorrhagic), 1 from infection and 1 from accidental trauma. Cohort characteristics and comparisons are summarized in Table 1. There were no differences between the two groups concerning age, gender and performance status. Disease characteristics were non-significantly different, except for higher leukocyte count in those who with early death. D-dimers levels at diagnosis and during treatment were higher for those with early mortality. Rates of infection and hemorrhage at diagnosis were similar in both groups.

Conclusions. Our cohort of real-life APL patients had an early mortality rate of 21%, mostly secondary to CNS vascular events. High leukocyte count and elevated D-dimers were the main determinants for early death. Although important advances were made in treatment, there is a need for better supportive care to avoid excess death at APL presentation.

TABLE 1: Characterization of cohort population and clinical and analytical variables. BCR, breapoint cluster region, BM, bone marrow, LDH, lactate dehydrogenase. * Mann-Whitney # X-square

		Induction survivors (n= 50)	Early Deaths (n = 13)	p value
Age median [min;max]		53 [24;78]	66 [33;80]	0.096*
Gender Female %		52	69	0.265#
Risk %	Low	18	15	**0.016#**
	Intermediate	66	31	
	High	16	54	
Platelets at diagnosis median [min;max]		20 [5;120]	23[5;106]	0.905*
White Blood Count median [min;max]		1.40[0.29; 66.84]	11.65[0.43; 178]	**0.006***
LDH median [min;max]		307 [132;1244]	308[297;901]	0.400*
Blasts BM % median [min;max]		80[65;95]	68[40;93]	0.829*
Caryotype %	t(15,17)	80	79	0.773*
	Normal	6	7	
	No metaphases	12	7	
	Unknown	2	7	
BCR %	BCR 1	56	31	0.099*
	BCR 2	6	0	
	BCR 3	36	62	
	Others	2	7	
D-dimers median [min;max]	At diagnosis	31[4;144]	46[8;81]	**0.024***
	Maximum	35[5;194]	65[7;187]	**0.012***
Fibrinogen median [min;max]	At diagnosis	156[68;396]	141 [65;310]	0.241*
	Nadir	127[56;277]	131[39;252]	0.728*
Infection at diagnosis %		36	61.5	0.096#
Hemorrhage at diagnosis %		76	84.6	0.506#

CO038
A MULTICENTER EXPERIENCE FROM LEBANON IN CHILDHOOD AND ADOLESCENTS ACUTE MYELOID LEUKEMIA: HIGH RATE OF EARLY DEATH IN CHILDHOOD ACUTE PROMYELOCYTIC LEUKEMIA

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Background. Acute myeloid leukemia (AML) is a disease with marked heterogeneity. Despite major improvement in outcome, it remains a life-threatening malignancy. Demographic and clinical data on pediatric AML is lacking among the Lebanese population.

Purpose. We aimed to identify clinical, molecular and outcome data in children with AML in Lebanon.

Methods. A retrospective chart review of children with AML diagnosed in 3 Lebanese hospitals during the past 8 years was conducted.

Results. From May 2002 through March 2010, we identified 24 children with AML in Saint George Hospital University Medical Center, University Medical Center Rizk Hospital and Abou-Jaoude Hospital. Males and females were equally represented; median age at diagnosis was 9 years (range 1-24) and median WBC at diagno-

sis was 31×10^9/L (range: 2.1-376×10^9/L). Twenty five percent of patients (6 out of 24) had acute promyelocytic leukemia (APL). Karyotype was normal in 33 % of patients; t(8;21), inv (16), t(8;9), t(7;11), t(9;11), complex chromosomal abnormality, monosomy 7 and trisomy 8 were the most common cytogenetic abnormalities encountered. Patients were treated on different European and North American protocols. Twelve patients (50%) achieved morphologic CR after cycle 1, 6 of them (50%) had bone marrow relapse within 11 months from diagnosis. Nine patients underwent allogeneic stem cell transplant and 3 of them are alive at 5 years post-transplant. Early death rate was 16.6% of patients, mainly those with APL and a presenting WBC > 10×10^9/L. Fifty per cent of APL patients had an early death due to DIC and delay in starting ATRA therapy. Overall, median survival for AML patients who died from disease progression was 25.8 months (range: 1-60 months). Overall disease-free survival was 30.4%. Patients < 10 years of age had a 50% survival rate compared to 0% in patients > 10 years.

Conclusions. Our report highlights the needs in Lebanon for better supportive care of children with APL including faster ATRA administration and aggressive transfusions, faster access to stem cell transplant for high-risk AML patients and the need for a national homogenous treatment strategy for children with AML.

Key words. AML, pediatric AML, leukemia, AML Lebanon.

CO039
EARLY DEATH RATE IN ACUTE PROMYELOCYTIC LEUKEMIA - A SINGLE COMMUNITY CENTRE EXPERIENCE IN SOUTH INDIA

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Background. Acute Promyelocytic Leukemia (APL) is a subtype of AML and comprises 5-8% of AML. APL is characterized by distinctive blast cell morphology, and other unique features like, life threatening coagulopathy, potential for chemotherapy induced complete remission and unique sensitivity to all –trans-retinoic acid (ATRA) and arsenic. Despite the sensitivity of APL to differentiating agent ATRA, early death secondary to intracranial or pulmonary haemorrhage either before or during induction treatment remains the most vital cause of failure in the treatment of APL. As per the data from the major clinical trials, the induction death rate within the first month of starting ATRA ranged between 5%-10%, however in population-based studies (including patients who never enrolled in trials), the early death rate ranged between 17%-30%. We reviewed the clinical course and treatment outcome of APL patients treated at our centre.

Materials. 49 patients with APL were diagnosed at our centre over a period of 4 years 6 months (January 2013 to June 2017). 41 patients received induction therapy as per the standard protocol.

Results. Out of 49 patients, 31 patients were males and 18 patients were females with a male to female ratio of 1.7: 1. The median age for males was 40 years and for females was 21 years. 15 patients presented with upfront clinical presentation, of which ten had intracranial bleed (66.6%), two had intrapulmonary haemorrhage, two had bilateral pneumonia and one had cerebrovascular accident. 25 were assigned as high risk, 21 as intermediate risk and 3 as low risk. Seven out of 49 patients died within twenty four hours and only one out of them could receive the ATRA. Four out of 49 patients died within seventy two hours and only two out of them could receive the ATRA. A total of 41 out of 49 patients received ATRA or ATRA+induction therapy. As three out of these 41 patients succumbed to death within 72 hours in view of their critical clinical presentation, only 38 patients are considered to have received proper induction treatment. Six out of 38 patients (15.8%) had died during the course of induction treatment. The cause of death for all the six patients were attributed to gastrointestinal bleed in two and the rest had multifocal space occupying lesions in the brain, febrile neutropenia, pulmonary haemorrhages and differentiation syndrome respectively. One patient had a relapse during follow up, had undergone bone marrow transplantation and is now completely disease free. One patient was lost for follow up after induction treatment. Complete remission was achieved in 84.2% of cases.

Conclusions. APL is a curable haematological malignancy. The overall outcome in our study at a community level is comparable to the International studies; however there is a slightly higher early death rate, when compared to clinical trials data. Death during induction is most frequently related to the hemorrhagic diathesis and hence improvement in the early death rate in APL is warranted. This can be achieved by quicker diagnosis and enhanced efficient care. There should also be a high level of continuous medical education regarding the diagnosis of APL among the clinicians, to facilitate prompt suspicion, induction of appropriate supportive care and early referral to oncology centres.

Key words. APL, Induction deaths, ATRA

Posters

PO000
MUTATIONAL PROFILE OF RELAPSE-RISK GROUPS IN ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS

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Background. Although the fusion oncogene PML-RARA is known to initiate acute promyelocytic leukemia (APL), other cooperating mutations have also been implicated in the disease pathogenesis. However, the spectrum of mutations of APL patients within the relapse-risk groups, based on patient leukocyte and platelet counts at diagnosis, are not yet known.

Aims. 1) To identify genetic alterations that might cooperate with PML-RARA in the leukemogenic process within the three APL relapse-risk groups. 2) To find mutations at diagnosis responsible for poor outcome by comparing patients who experiment relapse vs. patients who do not relapse in each group.

Methods. We performed multi-amplicon targeted deep sequencing on bone marrow samples of 91 patients diagnosed with APL (PETHEMA LPA99/2005/2012) with a median follow-up of 2.8 years (range 0.2-10) (Table 1). APL patients were classified into relapse-risk groups according to initial leukocyte and platelet counts (Score Sanz *et al*. 2000). Libraries were prepared by TruSight Myeloid Panel (Illumina) that assesses 54 myeloid related genes. Paired-end sequencing was performed on a MiSeq (Illumina). Minimum depth for reliable analysis was fixed in 100x and minimum variant allele frequency (VAF) in 5%. FLT3-ITD mutations were analyzed by fluorescent PCR and capillary electrophoresis. Sequences obtained were analyzed with VariantStudio v2.1 software (Illumina) and IGV (Genome Browser).

Results. Distribution of 91 patients in the 3 relapse-risk groups was: 28 in low-risk group (31%), 48 in intermediate-risk (53%) and 15 in high-risk (16%). We found 150 mutations in 31 genes, in 73 out of the 91 patients included (a median of 1 mutation per patient (range: 0-5) with a mean read depth of 10360x. Eighteen patients remained wild-type for all analyzed genes (Figure 1). Only one of this patients suffered relapse (5%). In the global series, no single mutation or functional category showed an association with clinical variables or prognostic impact in terms of overall or relapse-free survival (RFS). There were no differences in the mean number of mutations per patient in each risk group (p>0.05). Patients who lacked mutations belonged to intermediate (13/48, 27%) and low risk (4/28, 14%) groups, except only one patient (1/15, 6%) in the high-risk group. FLT3 was the most frequently affected gene in high risk subgroup (10 mutated patients out of 15): 8 with FLT3-ITD and 2 with substitutions at codon D835. Seven patients classified as intermediate-risk relapsed (7/38, 18%). All but one carried mutations reported as unfavorable in AML (FLT3, PTEN, ASXL1, CUX1 and WT1). By contrast, patients who remain in complete remission in this group, lacked mutations with a greater frequency (12/31, 39%). Finally, within the low-risk group, 3 patients suffered relapse (3/27; 11.5%) and all of them presented at diagnosis missense mutations in the Ras domain of NRAS gene (p.Ser65Arg & p.Gln61Arg). Therefore, we could identify a small subgroup of patients at a very high risk of relapse (RFS at 5 years, 25% vs. 100%, p<0.001).

Summary/Conclusion. In summary, the present study shows that the mutational status of FLT3 and NRAS genes could be used as genetic marker for prognosis in APL, especially in the intermediate and low-risk groups, allowing a more accurate patient risk classification. Our data suggests the need to search for new mutations required for progression in APL, in order to benefit from a change in post-remission therapy.

Table 1. Clinical and biological characteristics of 91 APL patients.

	Global serie N=91	Low risk n=28	Intermediate risk n=48	High risk n=15
Age (years)	49,6±19,4	52,7±23,4	50,7±16,8	47,4±21,5
Male Sex, N (%)	48/91(53)	17/28(61)	24/48(50)	7/15(47)
BM blasts (%)	75±18	70±19	75±17	83±15
WBC count (x10^9/L)	8,7±18,3	2±1,5	2,6±2,6	37,4±24,8
Platelets (x10^9/L)	38,9±32,4	73,3±33	19,6±9,4	27,8±19,6
Hemoglobin (g/dL)	9,9±2,3	10,3±2,4	9,4±2,2	10,8±2,4
FLT3 mutations, N (%)				
ITD	14(15)	2(7)	4(9)	8(53)
D835	10	2(7)	6(14)	2(2)
CR rate, N (%)	78/86(90)	27/28(96)	38/43(88)	13/15(86)
Relapse rate, N (%)	12/79(15)	3/27(11)	7/38(18)	2/13(15)
PML-RARa isoform				
bcr1	60	20	31	9
bcr2	6	2	4	0
bcr3	25	6	13	6

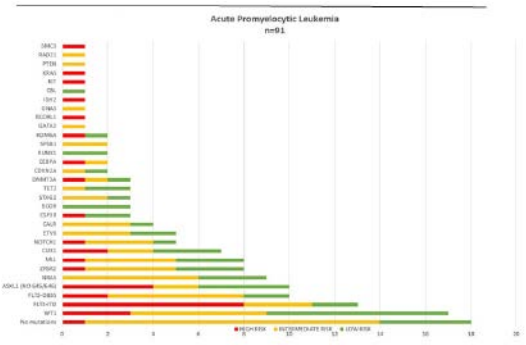

Figure 1. Mutational landscape in three risk APL subgroups.

PO001
THE SIGNIFICANCE OF ARSENIC INDUCED PML PROTEIN SOLUBILITY CHANGE

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Arsenic trioxide (As_2O_3) has recently become one of the most effective drugs for treatment of patients with acute promyelocytic leukemia (APL). The probable explanation for As_2O_3-induced APL therapy is the direct targeting of PML-RAR (P/R) oncoprotein by As_2O_3, which results in initiation of P/R degradation. The PML protein degradation by As_2O_3 occurs mainly through two steps: 1) Solubility change of PML or P/R fusion proteins (*i.e.*, soluble PML protein changes into insoluble protein); 2) As_2O_3 increases insoluble PML protein SUMOylation and ubiquitination through proteasome-mediated degradation pathway. Here, we attempted to detect alterations in solubility and modification of PML and P/R fusion proteins in pellet fractions of PML and P/R-transfected cells. For instance, cells were exposed to As_2O_3 for 3h and then washed thoroughly to remove As_2O_3, and further cultured for 6~24h in fresh medium. Interestingly, when arsenic was removed form medium of PML and P/R-transfected cells, PML and P/R proteins were appeared in the soluble fraction again, implying that PML or P/R protein solubility change might be a reversible process. Thus, in order to understand whether the shift of PML protein from insoluble to the soluble faction is dependent on newly translated proteins, cycloheximide (CHX), a protein synthesis inhibitor, was used to inhibit the new PML protein synthesis. Surprisingly, CHX completely inhibited recovery of PML or P/R fusion protein to the soluble fraction after removing arsenic, demonstrating that arsenic induced solubility change is irreversible. Our findings indicate that once arsenic induced the PML and P/R protein solubility changes, these insoluble PML proteins will be degraded even without continues arsenic exposure. However, PML or PML-RAR protein can be newly generated in cells after removing arsenic, suggesting that great caution should be taken in clinical therapy of APL patients before ending treatment of arsenic.

PO002
DEVELOPMENT OF A COMBINATION STRATEGY BASED ON ER AND OXIDATIVE STRESS IN ACUTE MYELOID LEUKEMIA

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Promyelocytic leukemia (APL) is characterized by the chromosomal translocation t(15:17) that results in the expression of the chimeric protein PML-RARα. The fusion of PML, a tumor suppressor that is the major component of the PML-nuclear bodies, with the Retinoic Acid Receptor-α arrests the differentiation program driven by RARα, blocking the leukemic blasts at the promyelocytic stage. Pharmacological doses of Retinoic Acid (RA) are able to remove the block, resume granulocytic differentiation and partially degrade PML-RARα leading to reformation of nuclear bodies. The association of RA with chemotherapy or with arsenic trioxide (ATO), the latter efficiently targeting PML-RARα for degradation, results in high cure rates of acute promyelocytic leukemia (APL). Despite showing a considerably improved safety profile, either RA or ATO are not devoid of toxicity, with the most important and potentially life-threatening one being the so-called retinoic acid differentiation syndrome. We show here that RA-induced differentiation of human APL cell lines and primary blasts dramatically increases their sensitivity to ER stress inducing drugs, like Tunicamycin (Tm), at doses that are not toxic in the absence of RA. Importantly only human progenitors cells derived from APL patients resulted sensitive to the combined treatment with RA and Tm whereas those obtained from healthy donors were not affected. Granulocytic differentiation of APL cells driven by RA triggers a physiological Unfolded Protein Response, a series of pathways emanating from the ER in case of ER stress, which ensues when higher protein folding activity is required as during differentiation. Although mild, the ER stress induced by RA is sufficient to render differentiating APL cells very sensitive to low doses of Tm. We also show that the UPR pathway downstream of PERK plays a major protective role against ER stress in differentiating cells and, by using a specific PERK inhibitor, we potentiated the toxic effect of the combination of RA and Tm. Moreover we found that low amounts of pharmacologically induced ER stress are also able to strongly increase ATO toxicity even in the absence of RA. Indeed the combination of ATO with Tm efficiently induced apoptosis in RA-sensitive and RA-resistant APL cell lines, at doses ineffective in the absence of ER stress. Eventually, we demonstrate that insurgency of oxidative stress, tightly linked with the UPR, is at the basis of the toxicity induced by Tm in combination with RA and/or ATO. In conclusion, our findings identify the ER stress-related pathways as potential targets in the search for novel therapeutic strategies in AML.

P0003
CLINICAL CHARACTERISTICS AND TREATMENT OUTCOME OF ACUTE MYELOID LEUKEMIA WITH UNCOMMON RARA FUSION VARIANTS

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Background. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by the translocation t(15;17) (q22;q21) generating the PML-RARA fusion gene. In rare cases of AML with APL like-morphology, RARA can be fused to an alternative partner other than PML (e.g. PLZF, NPM1, NUMA1, STAT5B, PRKAR1A and others) and this genetic heterogeneity accounts for the different sensitivity to targeted agents such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).

Patients and Methods. We collected data on 17 patients with AML characterized by variant RARA fusions, diagnosed between 2005-2017 from 13 institutions in US, Europe, Brazil, India and Australia. Of the 17 patients, 14 harboured PLZF-RARA, 1 PRKAR1A-RARA, 1 STAT5b-RARA rearrangements and 1 t(11;17)(q23;q21) with rearranged RARA (FISH).

Results. Morphologic data were compatible with classical M3 AML in all cases, and 38% presented with laboratory signs of coagulopathy. Flow cytometry was available in 12/17 cases and was compatible with classical APL, with 5/12 patients (42%) expressing CD56. Three cases were therapy-related AML due to previous exposure to radio-chemotherapy for solid tumors. Complete clinico-biological data are shown in Table 1. Most patients were adults (age range, 28-83 years) and two were younger than 18 years. Median WBC and platelet counts were 15.7 $\times 10^9$/L (range, 2.18-248) and 69×10^9/L (range, 26-170), respectively with 53% of patients presenting with WBC $>10 \times 10^9$/L. Fourteen out of 17 patients received induction with ATRA + chemotherapy (CHT), either intensive or low-dose based on age and performance status. In addition, one patient received ATO combined with CHT and ATRA, 1 CHT alone and 1 ATRA alone. After induction, 11 patients achieved complete morphologic CR (of whom 2 after a second induction cycle), 2 are currently in partial remission, 1 died early due to acute renal failure and 3 had resistant disease and received re-induction therapy that resulted in progressive disease (2 cases) and stable disease (1 case). Overall, the CR rate after induction was 65%. Of the 13 patients who underwent consolidation therapy, 8 received ATRA+CHT, 2 CHT alone, 2 gemtuzumab ozogamicin (GO), and 1 azacytidine. Five of these patients underwent subsequently allogeneic HSCT in first CR (2 from MUD and 3 from HLA-id sibling donors). A total of 4 patients relapsed during follow-up (1 STAT5b-RARA and 3 PLZF-RARA). Of these, 1 died of disease progression, 2 are is alive in CR2 and CR4 and 1 is currenly undergoing salvage therapy. With a median follow-up of 11 months (range: 1-86), 12/17 patients are alive (70.5%); of these, 9 are alive in CR, 2 are alive in partial remission and 1 in stable disease. 5/17 (29%) patients died due to disease progression (3 patients), transplant-related complications (1 patient), acute renal failure during induction therapy (1 case).

Conclusions. Despite the reported poor sensitivity of these RARA variants to standard APL therapy, this series suggests a relatively favorable outcome after treatment with ATRA combined with AML-like regimens including, in younger patients, allogeneic HSCT.

Table 1.

Table legend.

*CR, complete remission; **mCR, molecular complete remission;+Res, resistant disease; °ED, early death;§PR, partial remission

ATRA, All-trnas retinoic acid; IDA, idarubicin; DNR, daunorubicin; GO, gemtuzumab ozogamycin; ARA-C, cytaranine; L-DAC, low-dose cytarabine; HiDAC, high-dose cytarabine; MTZ, mitoxantrone; ETO, etoposide; ATO, arsenic trioxide;

HSCT, hematopoietic stem cell transplantation;MUD, matched unrelated donor

UPN	Age	Sex	Flow cytometry	WBC	Plts	Fibrinogen	Karyotype	Genetics	Induction	Consolidation	HSCT in 1st CR	Relapse	Outcome (months after diagnosis)
1	74	M	CD13+,CD33+,MPO+, CD34,CD56-,HLA-DR-, CD117-	5.3	93.0	Normal	47,XY,+22 [5] /46,XY[30]	PRKAR1A-RARA	ATRA+IDA+ATO, **CR***	ATRA+ARAC+Amsacrine	None	None	Alive in CR1, 15m
2	17	M	MPP+CD13+,CD33+, HLA-DR-,CD34-	2.1	170.0	84mg/dl	46,XY,inv(9)(p11q12)[19],46,XY, del(5)(q13q33),inv(9)(p11q12)[1]	STAT5B/RARA (FISH)	ATRA+AML-BFM 04, **CR***	AML-BFM 04	None	2 relapses (24 mos)	Dead, 41 m
3	56	M	NA	-	-	NA	46,XY,t(11;17)(q23;q12)[20]	FISH:RARArrearranged	ARAC+IDA, **CR***	GO	None	None	Alive in CR1, 24m
4	14	M	CD33+,CD13+,CD117+, MPO+,CD56+,HLA-DR, CD34-	20.0	138.0	85mg/dl	46,XY,t(11;17)(q23;q21)[18],RARArear	PLZF-RARA	ATRA+ICE, **mCR****	ATRA+GO	**HLA-id sibling**	None	Alive in CR1, 86m
5	52	M	NA	7.83	94.0	89mg/dl	46,XY,t(11;17)(q23;q21)[20]	PLZF-RARA	ATRA+ARA-C+DNR, Res	2nd IND:IDA+ ARA-C+GO,**CR**	**MUD**	None	Dead for TRM, 9m
6	50	F	CD33+,CD13+,CD117+, CD56+,CD34-,HLA-DR-	2.9	26.0	312mg/dl	46,XX,del(5)(q13q31),t(11;17)(q23;q21)[20], 46,XX[10]	PLZF-RARA	ATRA+ICE, **CR***	ATRA+MTZ+ ARA-C (2 cycles)	**HLA-id sibling**	None	Alive in CR1, 36m
7	67	M	CD33+,CD13+,CD117+, CD56+,CD34-,HLA-DR-	53.0	69.0	67mg/dl	46, XY, t(11;17) (q23;q21)[20]	PLZF-RARA	ATRA+IDA, **CR***	AIDA (high-risk)	None	None	Alive in CR1, 8m
8	33	M	NA	248.0	29.0	187mg/dl	46, XY, t(11;17) (q23;q21)[12]	PLZF-RARA	ATRA+DNR+ARA-C, **CR***	ATRA+DNR+ARA-C	**HLA-id sibling**	3 relapses (24 mos)	Alive in CR4, 53m
9	75	F	CD33+, CD117+, CD13+, HLA-DR-,CD34-	44.0	64.0	154mg/dl	46, XY, t(11;17) (q23;q21)[12]	PLZF-RARA	ATRA,**ED**[a]	-	-	-	Dead, 1m
10	83	M	NA	6.0	34.0	338mg/dl	46, XY, t(11;17) (q23;q21)[20]	PLZF-RARA	ATRA+L-DAC, **PR***	ATRA+L-DAC	None	None	Alive in PR, 2m
11	41	M	CD33+, CD13+, MPO+, CD117+, HLA-DR-, CD34-, CD56-	9.67	96.0	60mg/dl	46, XY, t(11;17) (q23;q21)[12]	PLZF-RARA	ATRA+IDA+ARA-C, **CR***	ATRA+HiDAC (2 cycles)	**MUD**	None	Alive in CR1, 11m
12	77	F	NA	8.0	-	NA	46, XY, t(11;17) (q23;q21)	PLZF-RARA	ATRA+DNR+ARA-C, **CR***	DNR+ARA-C (2 cycles)	None	1 relapse (36 mos)	Alive in CR2, 36m
13	38	F	CD33+,CD13+,CD117+, CD34+/-, HLA-DR-, CD56+/-	23.6	43.0	664 mg/dl	46,XX,t(11;17)(q23;q22)	PLZF-RARA	ATRA+DNR+ARA-C, **Res**	2nd IND: MTZ +ARAC+ETO,**Res**[§]	None	-	Dead, 3m
14	48	M	CD33+,CD13+, CD117+, HLA-DR, CD34-, CD56-	71.0	41.0	675mg/dl	No metaphases	PLZF-RARA	ATRA+DNR, **Res**[†]	2nd IND:ATO+ HiDAC ,**Res**[§]	None	-	Dead,6m
15	28	M	CD33+, CD13+, MPO+, CD34-, HLA-DR-, CD56-	23.8	113	NA	46, XY, t(11;17) (q23;q21)[13]/45, idem,-Y[10]/46,XY[3]	PLZF-RARA	ATRA+DNR+ARA-C, **PR***	2nd line:AZA,stable disease	None	-	Alive with stable disease, 7 m
16	36	M	CD33+, CD13+, CD117+,MPO+, CD34-, HLA-DR-, CD56-	11.5	40.0	NA	46, XY, t(11;17) (q23;q21)[10]/46,del(11)(q14) [3]/46,XY[7]	PLZF-RARA	DNR+ARA-C, PR*	3 HiDAC, CR	None	1 relapse (10 mos)	Alive in relapse, 11 m
17	76	M	CD33+,CD13+, CD117+, MPO+, CD56+, CD34-, HLA-DR-	44.0	140.0	171mg/dL	46, XY, t(11;17) (q23;q21) [15]	PLZF-RARA	L-DAC+ATRA, **PR**	L-DAC+ATRA	None	-	Alive in PR, 3 m

PO004
STROMAL-CELLS DOWNREGULATE MIR-23A LEVELS IN LEUKEMIC CELLS TO ACTIVATE PROTECTIVE-AUTOPHAGY AGAINST ARSENIC TRIOXIDE IN ACUTE PROMYELOCYTIC LEUKAEMIA

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The role of stromal micro-environment in drug resistance has been extensively reported for several cancers. We have demonstrated earlier that there is significant microenvironment mediated drug resistance (EMDR) to arsenic trioxide (ATO) in acute promyelocytic leukemia (APL) and that this was predominantly driven by up-regulation of the NF-kB pathway in the malignant cell. In our current study we have probed the molecular mechanism of ATO resistance in further detail. We undertook a study to evaluate the potential role played by miRNA in EMDR to ATO in APL. Using NGS based small RNA sequencing we identified hsa-miR23a-5p to be significantly downregulated in NB4 cells upon co-culture with HS5 stromal cells. We also observed that this miRNA is negatively regulated by NF-kB pathway and inversely correlated with NF-kB status in relapsed APL patients. These results were consistent with our earlier reported observations that NF-kB pathway is dysregulated and enhances drug resistance to ATO. We also observed miR-23a-5p mimics were able to restore the sensitivity of NB4 cells to ATO in the presence of stromal cells. Similarly, NB4/GFP-MAD cells (NF-kB inhibited cell line showing high expression of miR-23a-5p) also showed increased sensitivity to ATO even in the presence of stroma.

Looking for the targets of miR-23a-5p, we observed that there were no differences in the levels of known targets of miR-23a-5p at transcript levels in NB4 cells upon co-culture. Recent report suggested that miR-23a-5p can target autophagy pathway, hence we probed for autophagy pathway. We noted that there was an up-regulation of autophagy pathway in leukemic cells upon co-culture with stroma (where miR-23a-5p was downregulated). Re-introducing miR-23a-5p in the leukemic cells targeted autophagy pathway which was validated through western blot. We also observed that inhibiting autophagy by chemical inhibitors (bafilomycin A1 and hydroxychloroquine) along with ATO was also able to overcome EMDR to ATO. Finally, we were able to demonstrate a beneficial effect of autophagy inhibitor along with ATO in a transplantable APL mice model where a decrease in tumor burden on day20 was observed when compared to controls. Our results illustrates a complex molecular cross-talk between stromal cells and leukemic cells in protecting against the cytotoxic effects of ATO. This data along with that reported earlier by us illustrates multiple levels of regulation of the NF-kB pathway and resistance to ATO by stromal cell co-culture. Our work thus suggests that miR-23a-5p-mimics or autophagy-inhibitors could be an effective adjuvants along with ATO therapy in APL.

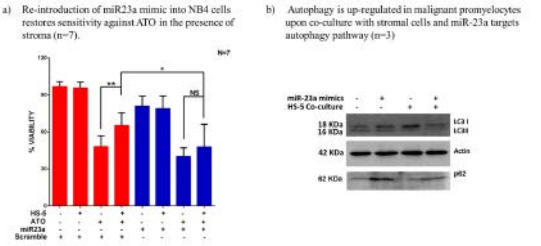

Figure 1.

PO005
METHYLATED ARSENIC METABOLITES BIND TO PML PROTEIN BUT DO NOT INDUCE CELLULAR DIFFERENTIATION AND PML-RAR PROTEIN DEGRADATION

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Arsenic trioxide (As_2O_3) is successfully used in the treatment of refractory or relapsed acute promyelocytic leukemia (APL), but its exact antileukemic mechanism in APL is still under investigation. The probable explanation for As_2O_3-induced cell differentiation is the direct targeting of PML-RAR oncoprotein by As_2O_3, which results in initiation of PML-RAR degradation. However, after injection, As_2O_3 is rapidly methylated in body to different intermediate metabolites such as trivalent monomethylarsonous acid (MMAIII) and dimethylarsinous acid (DMAIII), therefore, it remains unknown that which arsenic specie is actually responsible for the therapeutic effects against APL. Here we have shown the role of As2O3 (as iAsIII) and its intermediate metabolites (*i.e.*, MMAIII/DMAIII) in NB4 cells. Inorganic iAsIII predominantly showed induction of cell differentiation, while MMAIII and DMAIII specifically showed to induce mitochondria and endoplasmic reticulum-mediated apoptosis, respectively. On the other hand, in contrast to iAsIII, MMAIII showed stronger binding affinity for ring domain of PML recombinant protein, however, could not induce PML protein SUMOylation and ubiquitin/proteasome degradation. In summary, our results suggest that the binding of arsenicals to the ring domain of PML proteins is not associated with the degradation of PML-RAR fusion protein. Moreover, methylated arsenicals can efficiently lead to cellular apoptosis however; they are incapable of inducing NB4 cell differentiation.

PO006
FUNCTIONAL GENOMICS BASED APPROACHES FOR DISCOVERY OF NEW MECHANISMS IN ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia classified as M3. The APL patients have a high overall survival rate but there are some challenges in drug resistance, early mortality, relapse, and treatment-related complications. Exploring high throughput data in genomic era could leads to better understanding of background molecular mechanisms of the disease.

Methods. A genomic meta-analysis of available human gene expression profiles of APL patients against normal sample which derived from microarray experiments was performed. After quality assessment of raw data, differentially expressed genes determined and functional network and pathway analysis were performed.

Results. The gene expression analysis revealed a gene signature with 406 genes that are up- or down-regulated in APL. The pathway analysis determined that the MAPK pathway and its involved elements such as the JUN gene and AP-1 play important roles in APL pathogenesis, along with insulin-like growth factor–binding protein-7 (IGFBP7).

Conclusions. The results of this study reveals novel pathways and/or drug targets in the diagnosis and treatment of APL. The results of this meta-analysis could be useful for developing more effective therapy strategies and new biomarkers for diagnosis.

PO007
THE CANCER-ASSOCIATED HISTONE H3.3 K27M MUTATION BLOCKS CELLULAR SENESCENCE AND IMPARIS DIFFERENTIATION OF MOUSE HEMATOPOIETIC CELLS

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We have previously shown that disruption of PML-Nuclear Bodies by PML-RAR also leads to dispersal of the H3.3 Histone chaperone Daxx/ATRX and blocks murine bone marrow from entering cellular senescence, suggesting a role of H3.3 predisposition in senescence. Senescence usually limits proliferative capacity ex vivo. To further confirm this concept, now we have asked if alterations in H3.3 itself can affect senescence in the murine hematopoietic system. We have expressed the cancer-associated H3.3 K27M mutant in primary murine bone marrow and observed immortalization indicating a loss of replicative senescence. Also, H3.3 K27M expressing-cells rapidly outcompeted untransduced cells indicating accelerated proliferation.

Remarkably, the immunophenotype of these cells corresponded to LSK cells: Lin(-) Sca1(+)/cKit(+). We take this as evidence that H3.3 depositioning by the Daxx/ATRX Histone chaperone plays a role in differentiation as well as senescence. Taken together, these observations confirm and expand the postulated role of the PML domain of the APL- oncoprotein PML-RAR in leukemogenesis.

PO008
MISLEADING ACUTE PROMYELOCYTIC LEUKEMIA MORPHOLOGY AND IMMUNOPHENOTYPING: FIVE CASE REPORTS AND LITERATURE REVIEW

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We report five acute myeloid leukemia (AML) cases: 4 females and 1 male, aged 49, 62, 72, 74 and 59, with morphological features closer to the French-American-British (FAB) subtype M3 variant (M3v), who were observed between January 2005 and January 2017 at our institution. At diagnosis 4 cases had WBC count > 50×10^9/L (range 64 - 289×10^9/L) and in 4 cases coagulopathy was present. Peripheral blood blast cells had bilobed, convoluted nucleus and hypogranular cytoplasm, mimicking M3v blast cells. A low percentage of atypical promyelocytes was also observed. Whereas in bone marrow specimens a high percentage of granular and agranular myeloblasts were encountered, thus the diagnosis of AML with maturation subtype (FAB M2) was made. Cytochemistry showed high and intense expression of Myeloperoxidase (MPO > 90%) in all cases. As to immunophenotypic features, blast cells stained positive for CD33 and CD9, but negative for HLA-DR and CD34. In 3 out of 5 cases, CD56 was expressed. In no case the gene translocation t(15;17)(q2;q21) or the promyelocytic leukemia/retinoic acid receptor α rearrangement (PML/RARα) were detected. Nucleophosmin (NPM1) gene mutation was demonstrated in 3 cases, 2 patients showed both NPM1 gene mutation and fms-related tyrosine kinase-3 (FLT3) gene mutation of internal tandem duplication type (ITD).

Four patients died, and one patient refused any therapy and was lost to follow-up. Causes of death comprise che-

motherapy-induced aplasia during an intensive induction AML-GIMEMA schedule (2 patients) and pulmonary thromboembolism at the diagnosis (1 patient). Interestingly one patient (expressing NPM1 gene mutation) was treated with epigenetic therapy (low doses ARA-C+ATRA) obtaining blast cells differentiation, as observed in APL during ATRA-based treatment. This patient maintained stable disease for 10 months and then died for progression disease and sepsis.

Acute promyelocytic leukemia (APL) is a unique biologic and clinical entity characterized by PML/RARα gene rearrangement. Immunophenotype is characterized by low expression or absence of HLA-DR and CD34. The diagnosis is usually made on the basis of its morphologic features, flow cytometry, cytogenetic and molecular genetic investigations. The advent of molecularly targeted therapy with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) made this one of the most treatable form of AML. The existing literature describes three morphologic forms: hypergranular (the typical variant), hypogranular and hyperbasophilic. Only a few cases of AML were described in literature, morphologically characterized by blast cells similar to atypical hypogranular promyelocytes (M3v subtype) but lacked of t(15;17) and PML/ RARα rearrangement.

Our five cases suggest the existence of a distinct subtype of AML not yet classified, with transitional aspects between the AML with maturation (FAB M2 subtype) and M3v characterized by: leucocytosis, morphological and immunophenotypic findings close to atypical promyelocytic cells but lack of t(15;17) and PML/RARα rearrangement. Further studies are needed to confirm our hypothesis.

PO009
TRIB3 PROMOTES APL PROGRESSION THROUGH STABILIZATION OF THE ONCOPROTEIN PML/RARA AND INHIBITION OF P53-MEDIATED SENESCENCE

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Acute promyelocytic leukemia (APL) is characterized by a chromosomal translocation that fuses the promyelocytic leukemia gene with the retinoic- acid-receptor-alpha (RARA) gene to give an oncoprotein PML/RARA. Despite the combination of ATRA and chemotherapy or arsenic makes APL highly curable, relapsed and refractory APL, due to treatment resistance, still occur among all prognostic subgroups of APL patients. We recently report that TRIB3, a member of pseudokinase family and stress responsive protein, promotes APL progression through stabilization of the oncoprotein PML/RARA and inhibition of p53-mediated senescence. The elevated TRIB3 expression positively associates with APL progression and therapeutic resistance. Genetic ablation of TRIB3 eradicates APL by accelerating PML/RARA degradation. Mechanistically, TRIB3 interacts physically with the oncoprotein PML/RARA, and this interaction suppresses the sumoylation, ubiquitylation, and degradation of PML/RARA. Genetic depletion of TRIB3 expression or pharmacological disturbance of the TRIB3 and PML/RARA interaction with a cell-penetrating -helical peptide combined with ATRA/As2O3 attenuates or eradicates APL by restoring PML and PML/RARA sumoylation, PML nuclear body assembly and p53 mediated senescence. Our findings indicate that TRIB3 is critically involved in the pathogenesis of PML/RARA -driven APL, and that targeting TRIB3, particularly the TRIB3 and PML/RARA interaction, is a potential therapeutic option against APL.

PO010
PML NUCLEAR BODY DISRUPTION COOPERATES IN APL PATHOGENESIS, IMPACTING DNA DAMAGE REPAIR PATHWAYS

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Acute promyelocytic leukemia (APL) is driven by the oncogene PML-RARA, which is generated by fusion of the promyelocytic leukemia (PML) and retinoic acid receptor alpha (RARA) genes, and which strongly interferes with downstream signalling and the architecture of multiprotein structures known as PML nuclear bodies (NBs). NB disruption is a diagnostic hallmark of APL; however, the importance of this phenomenon has only been studied in vitro. Then, to address this, we generated a knock-in mouse model with NB disruption achieved through mutation of key zinc-binding cysteine residues (C62A and C65A) in the Pml RING domain. While no leukemias developed in Pml^C62A/C65A mice, the forced dimerization of RARα, mediated artificially by linking RARα to the dimerisation domain of the NFκB p50 subunit, in cooperation with NB disruption was associated with doubling in the rate of leukemia ($p<0.0001$), with a reduced latency period ($p=0.008$). Moreover, response to targeted therapy with ATRA significantly improved the survival of mice transplanted with Pml^WT-p50-RARα or PML-RARα leukemic blasts, but not with Pml^C62A/C65A-p50-RARα, revealing the

essential role of NB for an effective response to differentiating drug.

While formation of the PML-RARA fusion is considered an initiating event in APL pathogenesis, it is insufficient for the full leukemic phenotype. Exome sequencing studies have consistently identified presence of cooperating mutations. Since Pml and Pml NBs have established roles in DNA repair and in the maintenance of genomic stability, we speculated that loss of NB integrity could affect these functions. Whole exome sequencing revealed a trend of higher genomic instability in Pml^C62A/C65A-p50-RARα leukemia as compared to Pml^WT-p50-RARα, with detection of mutations found in human APL, including Kras, Ptpn11 and Usp9y. Using DNA repair reporter assays, we demonstrated that DNA repair via both non-homologous end joining (NHEJ; p=0.01) and homologous recombination (HR; p=0.006) pathways was less efficient in Pml^C62A/C65A primary cells than in Pml^WT cells. Importantly, using a PML-RARα-inducible cell line, comparable defects in the NHEJ and HR pathways, which were PML-RARα dependent, were identified. These data were also supported by an increase in sister-chromatid exchange (p<0.0001) and chromosome abnormality (p=0.0002) rates in the context of Pml^C62A/C65A versus Pml^WT. Interestingly, the kinetic of repair of ionising radiation (IR)-induced DNA double-strand breaks, assessed by analysis of γH2AX foci formation and clearance, was not affected. None of the DNA repair players analysed (*e.g.* Blm, Rad51 and 53BP1) failed to form foci in response to IR. However, their basal levels of foci were significantly greater in the presence of Pml^C62A/C65A (p<0.04; quantified using Amnis ImageStream^X Mk II imaging flow cytometer). Additionally, we found that Rad51 foci showed a defect in localisation post-IR when Pml^C62A/C65A was expressed, with impairment of Rad51 co-localisation and interaction with γH2AX. Altogether, our data therefore highlight the importance of re-formation of NBs for an efficient response to targeted therapy, the significant contribution of Pml NB to the effectiveness of DNA damage repair processes, and the manner in which their disruption mediated by the PML-RARα oncoprotein can assist APL pathogenesis.

PO011
HYPERTRIGLYCERIDEMIA IN NEWLY DIAGNOSEDACUTE PROMYELOCYTIC LEUKEMIA

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Objective. We conducted a retrospective study to investigate the lipid profiles andkinetics in patients with acute promyelocytic leukemia (APL).

Materials. We analyzed data from 160 newly diagnosed acute myeloid leukemia (AML) patients including 81 APL patients and 79 non-acute promyelocytic leukemia (non-APL) patients as controls. Serum lipid levels and other major clinical parameterswere recorded.

Results. Sixty-six percent of the APL patients had hypertriglyceridemia, whereas 32% of the non-APL patients had hypertriglyceridemia before receiving treatment (p=0.0003). The initial levels of triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) andlow-density lipoprotein cholesterol (LDL) in the APL patients were higher than those in controls (p<0.0001). In terms oflipid kinetics, the level of TG significantly increased in APL patients during induction treatment with all-trans retinoic acid (ATRA) and arsenic. The levels of TGand TC in non-APL patients decreased during induction treatment with idarubicin and cytarabine. Multivariable analyses showed that APL was an independent risk factor for hypertriglyceridemia in all patients (OR=3.2, 95% CI 1.63–6.31, p=0.01) before treatment. A high triglyceride level was not significantly associated with disease-free survival or overall survival in the APL patients.

Conclusions. The level of triglyceridesis significantly elevated in APL patients before treatment and increased during induction treatment.

PO012
MULTIDISCIPLINARY MANAGEMENT OF SEVERE ACUTE LIMB ISCHEMIA IN A PATIENT WITH ACUTE PROMYELOCYTIC LEUKAEMIA TREATED WITH ALL-TRANS RETINOIC ACID AND ARSENIC TRIOXIDE

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Patients with acute promyelocytic leukaemia (APL) have a higher risk to develop hemorrhagic and thrombotic complications before and during treatment. Thrombocytopenia, disseminated intravascular coagulation (DIC), direct hyperfibrinolytic mechanism and all-trans retinoic acid (ATRA) therapy, contribute to these clotting complications and, subsequently, to early death (ED) that ranges from 29% to 9,6% for hemorrhagic and thrombotic/embolic complications respectively.

Thrombotic events associated to APL are probably underestimated. In this setting, the arterial complications are slightly more common than venous complications. The three common type of major thrombosis are: deep vein thrombosis/pulmonary embolism, cardiac events and cerebrovascular accidents. Another rare arterial thrombosis threatening organ function is acute limb ischemia (ALI). ALI in APL has been reported only in 9 case report: about 44% were fatal and only one case was treated with the combination of ATRA and arsenic trioxide (ATO). A 66 old man referred to the emergency room for persistent and progressive leg pain since two weeks. Past medical history revealed: acute myocardial infarction (AMI) about ten years before, blood hypertension, dyslpidpidemia, diabetes mellitus and obesity. At the physical examination the left lower extremity appeared red, cold and there were not palpable distal pulses. The blood analysis revealed pancytopenia: white blood cell 720/mmc, hemoglobin 9,4 g/dL and platelets 123000/mmc; no evidences of DIC and all the other tests were unremarkable. Peripheral smear showed presence of

blasts with Auer rod. APL was suspected and ATRA was immediately started.

The patient was admitted to our hematology ward. The bone marrow evaluation confirmed diagnosis of low risk APL, cytogenetic analysis revealed t(15;17) with hypotetraploide karyotype, loss of chromosome 9, 14, 16; the molecular analysis showed the fusion transcript PML/RARa bcr3. Therefore, ATO was added to the therapy. The pain in his ischemic foot was severe and required a continuous intravenous (i.v.) infusion of morphine. Concomitantly antibiotics were started. The computed-tomographic angiogram (CTA) showed an obstruction of the tibial-peroneal trunk and plantar arteries. The surgical intervention was excluded by Vascular surgeons due to the high risk of infectious and hemorrhagic events: the progressive thrombocytopenia required a low molecular weight heparin, and the antiplatelets therapy was stopped. According to the cardiologist, despite the risk for the previous AMI, the patient started the i.v. prostaglandin.

Supportive treatment with platelets and red blood cells transfusions was administered. The patient didn't develop DIC or leukocytosis during the treatment. At the blood count recovery, the patient resumed the antiplatelet therapy and he underwent to bone marrow analysis that showed hematological and molecular complete remission. The patient developed a progressive gangrene in his foot and needed a surgical revascularization and amputation of the lower limb with thigh-stump packaging.

Three weeks later he started the consolidation program with ATRA and ATO. To date, the patient is under his second phase of consolidation therapy, no further lower limbs thrombotic complications arose.

The ALI is a rare thrombotic event in APL, there are no consistent data supporting the conservative versus surgical methods. The multidisciplinary care approach and patient tailored treatment are crucial.

PO013
ACUTE PROMYELOCYTIC LEUKEMIA CELLS UNDERGO ETOSIS TO EXACERBATE COAGULATION DISORDER

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Introduction. Despite treatment with all-trans-retinoic acid, the early death rate in unselected acute promyelocytic leukemia (APL) due to hemorrhage still remains unacceptably high. We have recently demonstrated that APL cells undergo a novel cell death program, termed ETosis, which involves release of extracellular chromatin (Ma R *et al.,* Cell Death Dis 2016). However, the role of promyelocytic extracellular chromatin in APL-associated coagulation disorder remains unclear. The aims of this study were to identify the novel role of extracellular chromatin in induction of a hypercoagulable state in APL and to evaluate its interaction with fibrin and endothelial cells (ECs).

Methods. Forty newly diagnosed APL patients were included. Fresh APL blasts from bone marrow specimens were treated with 1 M ATRA or phosphate buffered saline (PBS). ETosis was distinguished by rounded cells whose nuclei stained with PI and whose nuclear contents diffused throughout the cell. Cell-free DNA (cf-DNA) was quantified using the Quant-iT PicoGreen dsDNA Assay Kit. MPO-DNA complexes and TAT (thrombin-antithrombin) complexes were detected by ELISA. ECs were incubated in the presence or absence of 20-fold concentrated extracellular chromatin. Procoagulant activity (PCA) of ECs and APL cells was evaluated by one-stage recalcification time assay, pro-thrombinase assay and fibrin formation assay. DNase I or anti-TF were included in the inhibition assays.

Results. ATRA treatment induced markedly increased cf-DNA release in a time-dependent manner compared with no ATRA group. Furthermore, ETosis was the major cell death pattern in the ATRA-treated group while apoptosis was predominant in the no-treatment group until the third day, indicating that the increased cell-free DNA triggered by ATRA was mainly from ETosis. Additionally, thrombin generation was found to parallel the change in the releasing of promyelocytic extracellular chromatin induced by ATRA. Pretreatment with DNase I inhibited thrombin generation by 47%, diminished PCA by 35%, prolonged coagulation time, and attenuated fibrin formation by 50%, while neutralizing anti-TF antibody produced no effect. Patients had markedly increased levels of cf-DNA and MPO-DNA complexes compared to controls. Furthermore, baseline WBC counts were positively correlated to both plasma cf-DNA and MPO-DNA complexes. Plasma cf-DNA was negatively correlated with fibrinogen. Confocal microscopy showed that fibrin was preferentially deposited on promyelocytic chromatin from ETosis or apoptosis and exposed PS. Lastly, we found that extracellular chromatin from the ATRA group triggered PS exposure on ECs, converting them to a pro-coagulant phenotype. This cytotoxity was blocked by DNase I by 20% or activated protein C (APC) by 31% indicating that DNA scaffold and histones were both necessary for the cytotoxic effect of extracellular chromatin.

Conclusions. ATRA promotes procoagulant promyelocytic extracellular chromatin mainly through ETosis. Extracellular chromatin fosters excess thrombin generation, increases fibrin deposition, and causes EC damage. To improve the remaining coagulation disturbance in high-risk APL patients during ATRA administration, therapeutic strategies could focus on combined application of DNase I and APC to accelerate the degradation of released promyelocytic extracellular chromatin.

Disclosure of Interest: None declared.

PO014
UTILITY OF D-DIMER LEVEL AS A MARKER FOR DIFFERENTIATION SYNDROME, INFECTION, AND DEATH IN ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Acute Promyelocytic Leukemia (APL) is the most curable leukemia with reported survival >90% in large co-operative group studies. Induction-related deaths from bleeding, infection, and differentiation syndrome (DS) remain a threat with early death (ED) rate of 30%. DS is a unique and life-threatening complication of APL induction, characterized by unexplained fever, weight gain, pleuropericardial effusion, hypoxemia, hypotension, and/or vascular capillary leak syndrome leading to peripheral edema and acute renal failure. These pathophysiologic complications are sequelae cytokine release from malignant promyelocytes. This clinical diagnosis is without identifying markers. We report our observation on the utility of D-dimer level as a potential marker for the identification of DS, infection and death during APL induction.

Methods. We conducted retrospective chart reviews of APL patients treated at Emory University and co-managed at community and academic treatment centers throughout Georgia, South Carolina and bordering states from 7/2013 to 4/2017 with the purpose of decreasing ED. IRB approval was obtained. Elevations in D-dimer were based on laboratory specific reference values.

Results. 138 patients were enrolled in this study, of whom 44 patients (32%) developed DS and 18 patients (13%) developed infection during induction. We followed the D-dimer trends in those patients that had serial levels obtained throughout induction therapy. At time of presentation, 100% of patients had elevated D-dimer. As disseminated intravascular coagulation (DIC) corrected, there was a drop in D-dimer. D-dimer re-elevated in 6 patients prior to DS onset (14%), 9 patients on day of DS onset (20%), and 6 patients after DS onset (14%). 3 patients (7%) that developed DS had D-dimers that remained elevated at levels unquantifiable by lab testing. 4 patients demonstrated no re-elevation in D-dimer in relation to DS onset (9%). Data was not available to ascertain D-dimer correlation with DS onset in 16 patients (36%). Infection data was collected and patients who developed infection during induction, excluding viral etiologies and pneumonia/pneumonitis due to correlation and overlap with DS presentation, were included totaling 18 patients. Re-elevation of D-dimer was noted in 4 patients in correlation to infection onset (22%), no re-elevation was noted in 3 (17%), and data was not available in 11 patients (61%). 12 patients died due to induction-related complications. D-dimer was re-elevated in relation to timing of death in 7 patients (58%), remained unmeasurably high in 1 (8%), and data was not available in 4 patients (33%). Table 1.

Conclusions. D-Dimer is a marker of inflammation and is elevated in inflammatory processes. Most patients presenting with APL have high D-dimer levels secondary to DIC. A repeat elevation after an initial decrease might be a useful marker of foreboding complications in APL, including DS, infection, and death. As evidenced in our study, there remain a significant number of patients with inconsistencies in D-dimer serial monitoring or entire lack thereof. Given the impressive correlation between D-dimer and aforementioned complications that our review demonstrates, this supports incorporating D-dimer in daily lab monitoring as a standard of care. Our observations, if confirmed in larger studies, could be a valuable addition to identifying induction-related complications earlier and decreasing incidence of early deaths.

Table 1.

	Differentiation Syndrome	Infection	Death
Group A: Re-elevation prior to onset (1-3 days)	6	2	5
Group B: Re-elevation day of onset	9	1	2
Group C: Re-elevation after onset (1-3 days)	6	1	NA
Group D: Unmeasurable due to unquantifiable elevations by lab testing	3	0	1
Group E: No re-elevation D-dimer	4	3	0
Group F: Timing could not be ascertained from available documentation or due to inconsistencies in D-dimer serial monitoring	16	11	4

PO015
CEREBROVASCULAR INFARCTS IN THE SETTING OF DISSEMINATED INTRAVASULCAR COAGULATION AS PRESENTING SYMPTOM IN ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Patients with newly diagnosed Acute Promyelocytic Leukemia (APL) commonly present with disseminated intravascular coagulation (DIC) that can lead to hemorrhagic insult. Hematologists caring for APL patients understand that aggressive transfusion support with platelets, cryoprecipitate, and fresh frozen plasma must be initiated to correct the underlying DIC. Rarely, a patient with APL will present with arterial thrombosis in the setting of DIC and little is known about how to best manage these patients. On review of the literature, five cases were described where patients with newly diagnosed APL presented with CNS arterial thrombosis; 3 patients are alive with neurologic deficit and 2 are dead. (Table 1). We have experience with three patients diagnosed with APL who presented with cerebrovascular infarct. We report our experience to heighten awareness of this unusual presentation of this rare type of leukemia.

Methods. Chart review was conducted with IRB approval on three patients with known diagnosis of APL who presented to Emory University with signs and symptoms of stroke who were found to have ischemic cranial events. Demographics, past medical history, and treatment regimen for both infarction and APL were collected.

Case Series.

Patient 1. 21-year-old male who presented to an outlying hospital with expressive aphasia. MRI scan showed large right temporoparietal infarction. Labs

showed WBC 21.6, platelets 9,000, low fibrinogen, elevated PT and elevated d-dimer. High-risk APL was confirmed and ATRA and IV dexamethasone were started. Heparin drip was initiated to decrease risk of further ischemic insult. Worsening neurologic symptoms 4 days later led to a repeat MRI scan, which showed progressive right sided infarct and a new infarct in the left distal territory of the middle cerebral territory and expired shortly thereafter. Images 1 and 2 show infarcts on day 2 and 6 of admission.

Patient 2. 55-year-old female with presented with dysarthria and altered mental status. CT head showed left middle cerebral infarction and was immediately given tPA. Her admission labs showed WBC 37.6, platelets 48,000, PT 19, aPTT 35.3, Fibrinogen 67 and a diagnosis of high risk APL was established. She was induced with ATRA, Idarubicin and ATO and discharged in hematologic remission with no neurologic deficit.

Patient 3. 59 year old female, Jehovah's Witness, with multiple comorbidities presented with shortness of breath. Influenza A and PE were diagnosed and oseltamivir and warfarin was initiated. New left arm tingling prompted a brain MRI scan that showed multifocal bilateral acute infarcts. She was discharged with anticoagulation but readmitted 5 days later with a WBC of 38.4 and platelets 19,000. CT head showed progression of all the infarcts. APL was diagnosed and ATRA and ATO was started but she refused transfusions and died of neurologic deterioration.

Conclusions. Our case series review is consistent with the previous literature. The mortality in patients with APL presenting with CNS arterial thrombosis is extremely high. Since it is a rare occurrence in a rare malignancy, not enough is known on the best management strategy. More dedicated observation and research is warranted on this topic to improve outcomes in this otherwise very curable malignancy.

Table 1. Patients Presenting with CNS ischemic infarcts.

YEAR	AGE	SEX	PRESENTATION	TERRITORY	OUTCOME
1994	27	F	At Presentation	Unknown	Alive with deficit
1995	37	F	At Presentation	L MCA	Alive with deficit
1995	3	F	At Presentation	Unknown	Dead
2012	37	F	At Presentation	L ICA, MCA and ACA	Dead
2015	33	F	At Presentation	R MCA	Alive with deficit
* 2015	21	M	At Presentation	R MCA and lacunar infarct, L MCA	Dead
* 2014	55	F	At Presentation	L MCA	Alive, no deficit
* 2017	59	F	At Presentation	L PCA	Dead

P0016
A NORMAL PROTHROMBIN TIME, ACTIVATED PARTIAL THROMBOPLASTIN TIME AND FIBRINOGEN LEVEL DO NOT ELIMINATE DISSEMINATED INTRAVASCULAR COAGULATION AND BLEEDING RISK IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction. Acute Promyelocytic Leukemia (APL) is a rare but highly curable malignancy. Majority of APL patients present with disseminated intravascular coagulation (DIC) resulting in bruising, bleeding and occasionally life threatening hemorrhage. Hematologists frequently note the prothrombin time (PT), activated partial thromboplastin time (aPTT)and fibrinogen levels and, if normal, presume the patient does not have DIC. Our observations suggest that a normal PT, aPTT, or fibrinogen level do not eliminate DIC and bleeding risk in APL and that an elevated d-dimer is the more sensitive , but often under-utilized, indicator of DIC.

Methods. Retrospective chart review was conducted with IRB approval on patients diagnosed with APL and treated at Emory University and those co-managed at treatment centers in Georgia, South Carolina and neighbouring states as part of our initiative to decrease induction deaths. Patients managed from 7/2013 to 4/2017 were analyzed. The PT, aPTT, Fibrinogen, d-dimer levels, platelet count and signs of bleeding on the day of diagnosis were collected. Normal values were defined as PT <15.5, aPTT <36.5 and fibrinogen >200. Elevations in d-dimer were based on laboratory specific reference values.

Results. One hundred and thirty-eight patients were included in this analysis of whom 115 had d-dimer levels drawn on day of admission (day 1)and were elevated inall 100%. The median platelet count for these 138 patients was 31. Seventy-threeof the 138 patients (52.90%) presented with signs of bleeding including but not limited to: bruising, epistaxis, hematuria, hemoptysis, hematochezia and melena. Sixty-three patients (56.76%) had a normal PT and high d-dimer levels, while only 48 (43.24%) had a high PT and high d-dimer. Of the 63 patients with normal PTlevels, 54% had bleeding symptoms and the median platelet count for these patients was 40 (range 8 - 168). Forty-nine of 115 patients (42.6%) had normal fibrinogen levels on day 1. Notably, only six of the 138 patients included in this study presented with elevated aPTT levels. Twenty-seven patients did not have complete coagulation panels on the day of admission, and were omitted from the analysis. However of these patients missing either PT, aPTT, fibrinogen or d-dimer levels on day 1, 37%presented with signs of bleeding. Fourteen patients died during induction (Table 1).

Conclusions. All APL patients with available day 1 data had elevated d-dimer levels, even in the setting of a normal PT, aPTT and fibrinogen. An elevated d-dimer level was found to be the more sensitive indicator ofDIC. Over half of patients with normal PT levels presented

with signs and symptoms of bleedingand only six patients presented with abnormal aPTT levels. The most important observation is that a normal PT, aPTT, or fibrinogen level – combined or in isolation – does not eliminate the risk of DIC or life threatening bleeding. Hematologists must check a complete coagulation panel in suspected APL, including d-dimer, on day 1 and regularly thereafter. We theorize this will result in early recognition, prompt and aggressive management of DIC, and decrease early hemorrhagic deaths in this very curable malignancy.

Table 1.

Group	PT	aPTT	Fibrinogen	D-Dimer	Number	Induction Deaths
A	Normal	Normal	Normal	Elevated	33	3
B	High	Normal	Normal	Elevated	14	0
C	High	High	Normal	Elevated	2	1
D	Normal	Normal	Low	Elevated	27	2
E	Normal	High	Low	Elevated	3	0
F	High	Normal	Low	Elevated	32	4
G	Missing	Missing	Missing	Missing	27	4

PO017
DECREASING INDUCTION MORTALITY IN ACUTE PROMYELOCYTIC LEUKEMIA (APL) PATIENTS BELONGING TO THE JEHOVAH'S WITNESS CONGREGATION

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APL is a hyper-acute leukemia and presents withcytopenias and disseminated intravascular coagulation (DIC). The frustrating problem in APL in the general population is an early death (ED) rate of 30% due to bleeding, differentiation syndrome and infection. Jehovah's Witnesses (JW) offer a unique challenge by refusing transfusion; and yet despite their religious preferences, treatment goals remain the prevention of induction death and ultimately cure. Targeted drugs are available to treat APL with minimal myelosupression.Individualizing therapy with aggressive supportive care and erythropoietic growth factors is feasible in the Witnesses to prevent ED in this most curable leukemia.

Methods. We developed a model to include a set of streamlined treatment guidelines along with expert support to decrease induction deaths in both academic and community centers. We treated 3 patients and reviewed 9 published reports and summarize the outcome.

Results. Within our practice, patient 1 presented with anemia, thrombocytopenia and DIC and accepted cryoprecipitate but refused other blood products. All-trans retinoic acid (ATRA), arsenic trioxide (ATO), erythropoietin (EPO) and dexamethasone were initiated; but died due to profound anemia on day 7. Patient 2 presented with pancytopenia and DIC; ATRA and ATO were started. She accepted cryoprecipitate but no other blood products. Blood draws were limited, and darbepoetin was switched to erythropoietin with oral iron supplementation due to worsening anemia and angina with good response. She received consolidation and is in molecular remission 3.5 years post diagnosis. Patient 3 presented with anemia, thrombocytopenia and multiple infarcts per head CT scan. She initiated ATRA/ATO and agreed to cryoprecipitate only and died on day 2 from neurologic deterioration. Review of the literature was done to identify other similar cases (Table). Five of these twelve patients died during induction, three were high risk. All five of the deaths were due to symptomatic anemia. Five of seven surviving patients were treated with EPO prophylactically or after developing symptomatic anemia. Six patients received (ATRA) or ATRA/ATO, five of whom developed symptomatic anemia. The one who did not received EPO from day 1.

Conclusions. Our 3 patients and the 9 reported cases of (JW)demonstrate that the major cause of morbidity and mortality is non-hemorrhagic anemia. Therefore, the goal from the onset should be to prevent development or worsening of anemia with aggressive use of erythropoietic growth factors and iron supplements. ATO and ATRA cause minimal myelosuppression and if applied judiciously with aggressive supportive care, Witnesses can be safely induced and potentially cured.

Table 1. Induction of APL patients belonging to the (JW) congregation.

Pt#/ Year	Age/ Sex	Risk status	Induction	Initial Hb	Supportive care	Complications	F/U months	Death
1/1990	18/F		Chemotherapy	7.5	Tranexamic acid, Aprotinin, Norethisterone	Anemia		YES
2/1994	28/F	Intermediate	ATRA	6.2	G-CSF, EPO	Pregnancy, Anemia	12	NO
3/1997	10/M	Intermediate	ATRA/Ara-C	8.0	EPO	Anemia	9	NO
4/1998	28/M	High	ATRA/Ara-C	6.9	EPO	Anemia		YES
5/1999	17/F		ATRA/IDA					NO
6/2000	62/F	Intermediate	ATRA	7.0	EPO		120	NO
7/2004			ATRA, Dauno, Ara-C				32	NO
8/2007	39/M	Intermediate	ATRA/ATO	8.5	EPO	Myocardial infarction; Anemia	36	NO
9/2013	71/F	High	ATRA/ATO	6.6	EPO	Anemia		YES
10/2013	56/F	Low	ATRA/ATO	11.8	Darbopoetin, EPO	Anemia, Angina	12	NO
11/2014	28/F		ATRA	10.5		Pregnancy, Anemia		YES
12/2014	59/F	High	ATRA/ATO	7.4	EPO	Stroke		YES

ABBREVIATIONS: Dauno- Daunorubicin; Ida Idarubicin; Ara-C- Cytarabine; 6-Thio- 6 Thioguanine; Hb- Hemoglobin

PO018
COMORBID CONDITIONS IN NEWLY DIAGNOSED PATIENTS WITH APL IN GEORGIA, SOUTH CAROLINA AND NEIGHBORING STATES IN THE USA; DECREASED INDUCTION MORTALITY DESPITE A HIGH COMORBID INDEX

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Background. Comorbid conditions have an effect on outcomes in many diseases. Acute promyelocytic leukemia (APL), a subtype of AML, is highly curable with a long term survival rate as high as 90% in large clinical trials treated on a protocol. However survival in the general population is much lower with an induction mortality of 30%. A high comorbid index has been linked to increased deaths and decreased survival in several hematologic malignancies including AML, MDS, CML, multiple

myeloma and NHL. There is published data on older patients with APL and exclusion due to poor health or multi-morbidity but there is limited literature on how comorbid conditions impact induction mortality in APL.

Hypertension and obesity are prevalent in >30% of Georgia (GA) and South Carolina (SC) residents according to 2014 CDC data, and these and other conditions were prevalent among our patient population. We sought to quantify comorbidities in patients with newly diagnosed APL and assess if it had an effect on early death.

Methods. We performed a retrospective chart review with IRB approval of 138 patients treated at leukemia treatment hospitals in GA, SC and neighboring states. These centers had access to a simple two-page APL treatment algorithm we developed as well as expert support designed to decrease induction mortality. We used the Combined Age-Charlson Comorbid Index (CA-CCI), a tool utilized as a measure of mortality risk based on comorbidity which accounts for age as an independent risk factor for mortality, assigning additional points for age ≥50. The CCI assigns weights of 1-6 to comorbidities including but not limited to hypertension, Type II diabetes, renal impairment and then an overall score is calculated; the higher the score, the higher the mortality risk. We also tracked obesity as a separate condition, as it is not included in the CCI. Statistics are descriptive and survival analysis was performed by SPSS version 24; overall survival curves were obtained by Kaplan-Meier analysis.

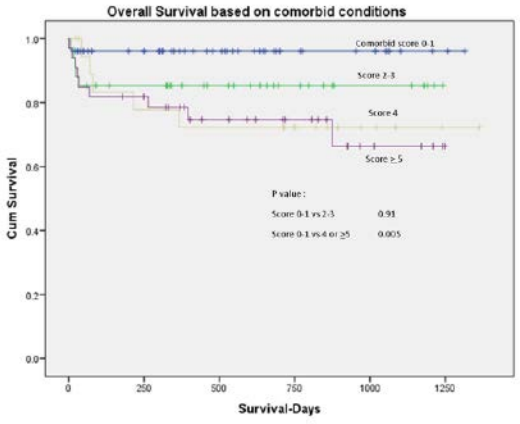

Figure 1.

Results. Between 7/2013 and 4/2017, 138 patients were treated at 4 large leukemia centers and 30 community hospitals.129 (93%) patients had one or more comorbid conditions, excluding age. Obesity was the most prevalent (n=85, 62%), followed by hypertension (n=75, 54%). Based on the CA-CCI calculation, 24.64% (n=34) had a score of 2-3, 14.49% (n=20) had a score of 4, and 23.91% were highest risk with a score of ≥5 (n=33).The remaining 36.96% (n=51) had a risk score of ≤1 (lowest risk).

There were 12 induction deaths (8.7%).Two patients were lowest risk with a score of ≤1,five scored 2-3, one scored4, and four were highest risk with a score ≥5. Eight of the 12 patients who died were obese. Overall, we found our induction mortality rate of 8.7% to be low compared to nationally published data in APL.

Conclusions. Patients treated for APL in GA, SC and neighboring states from 2013–2017 had a high incidence of comorbid conditions at presentation. We felt it was important to also highlight that a majority had concomitant obesity, a comorbidity linked to poor prognosis in many diseases including APL. In spite of the majority of our patients having multiple comorbidities and nearly a quarter having a CA-CCI score of ≥5, our induction mortality was low. Given our relatively small number of deaths, we believe that in APL patients with multiple comorbid conditions, our treatment algorithm combined with expert support has decreased induction mortality.

PO019
FOLLOW-UP AND OUTCOME OF TWELVE-YEAR EXPERIENCE IN ADULTS PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterized by the accumulation of abnormal promyelocytes in bone marrow and/or peripheral blood. The clinical course of APL has been modified in recent years, from rapidly fatal acute leukemia to one of the curable subtypes of AML. The introduction of therapeutic agents that act directly on the molecular changes, such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) had a major impact on APL patient survival, which is around 70-90%. The presumptive diagnosis of APL should be quick, because these patients are at risk for early death. The incidence of ALP in Brazil is higher (20%) than in the United States and Western Europe (5-15%). The slightly high mortality rates, especially early mortality, motivate studies to understand this pathology in the Brazilian context. Some known adverse prognostic factors have been used as a guide for intensifying the treatment, such as the criterion by Sanz, which is based on thrombocytopenia ($<40\times10^9$/L) and especially on hyperleukocytosis ($>10\times10^9$/L). Nevertheless, additional prognostic factors are still being studied that can negatively impact the course of the disease, namely: CD34 expression, high value of lactate dehydrogenase (LDH), mutations in the gene FLT3, severe bleeding, high disseminated intravascular coagulation (DIC) score, anemia (hemoglobin <10 g/dL), hipogranular APL, additional chromosomal abnormalities (ACAs), PML-RAR transcript bcr3. For this, it was analyzed retrospectively the laboratory and clinical findings of 44 brazilians patients with APL diagnosed and treated at the Hematology Service of the University Hospital of the Federal University of Santa Catarina (HU-UFSC) between 2001 and 2013. The according with

results, the patients were classified following: risk group (PETHEMA system), performance status, coagulation disturbance, DIC score, and prognostic factors such, expression of CD34, FLT3 mutations, APL hipogranular, ACAs, value of hemoglobin, LDH. The response of treatment was evaluated during induction, consolidation and maintenance, and the occurrence of relapse and death.

APL corresponded to 25% of all AML cases in this study. Of the 44 patients studied, 37 (87.8%) had complete remission. Over two years, overall survival (OS), disease-free survival (DFS), event-free survival (EFS) and risk of hematologic relapse (RR) were 77.2%, 67.4%, 67.4% and 8.3%, respectively. Early mortality occurred in 15.9%, representing 78.9% of total APL deaths. The greatest cause of death was severe bleeding, especially in the central nervous system (CNS). In multivariate analysis with logistic regression, the prognostic factor influencingresponse to therapy were the absence of sepsis (p=0.007). The prognostic factor that most influenced death was severe bleeding (p<0.0001). Adjusting for this adverse factor, the survival probability was 89% in two years. The best therapeutic response was achieved in patients without sepsis (odd ratio=9.667). Early mortality represents almost all deaths and severe bleeding was the most important event leading to death. Recognizing high-risk patients is crucial more aggressive support measures are implemented aiming to preventing an unfavorable outcome. Thus, it is concluded that the clinical outcomes of APL patients at our brazilian single center is adequate and comparable to large centers.

PO020
DECREASING EARLY DEATHS (ED) IN APL IN THE "REAL WORLD". THE GEORGIA AND SOUTH CAROLINA (USA) EXPERIENCE

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Background. APL is a highly curable malignancy with survival >90% in multi-center studies. However these spectacular results are not reproducible in the general population. Population based studies from Swedish Cancer Registry, Brazil and US SEER data showed that early deaths (ED) areas high as 30%, leading to a considerably lower survival compared to clinical trials where ED is approximately 5%. Decreasing ED remains a frustrating global challenge and the highest priority at all APL treatment centers and willimprovepopulation wide survival in this most curable leukemia. We report results of ourprospective trial using a set of simplified treatment guidelines along with expert support designed to decrease ED.

Methods. A network of leukemia treatment centers was established in Georgia, South Carolina and neighboring states.An aggressive outreach effort was made by visiting most of the centers to publicize the concept and educate hematologistsin the community about ED in APL. The protocol provides a simplified two page treatment algorithmthat emphasizes quick diagnosis, prompt initiation of therapy and proactive and aggressive management of the major causes of induction deaths. Expert and treating physician communication was established early when a diagnosis of APL was suspected and was maintained until the completion of induction.The study was IRB approved and consent was obtained upon confirmation of APL with no exclusion criteria. With funding from the Lymphoma Leukemia Society, patient accrual was initiated in July 2013 and continued till May 2016 when the accrual goal of 120 was met on an intent to treat basis.Statistics are descriptive.

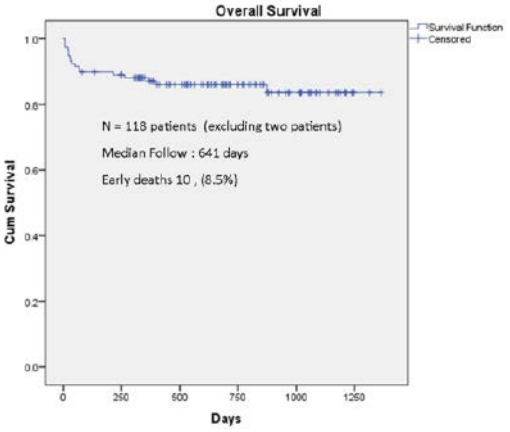

Figure 1.

Results. Between 7/2013 and 5/2016, 120 patients were enrolled at 5 large leukemia centers (n=54, 45%) and 24 community hospitals (n=66, 55%). Only 3 hospitals treated more than 3 APL patients/year. Median age was 54 years (range 21-84 years). 68 were male. 84% were low risk (WBC < 10,000/mm^3) and median WBC count was 4.3 (range 0.3-170,000/mm^3). ATRA was initiated at suspicion of APL in 100% of patients and was the only treatment in 2(1.5%). Arsenic was combined with ATRA in 93 (81.5%) patients while the other 17% received chemotherapy. 15(13%) had bleeding complications at presentation. Treatment course was complicated by infection and DS in 31(28%) and 40(34%) patients respectively.

There were 12 early deaths; 1 was a Jehovah's Witness who declined transfusions and 1 was enrolled 12 days after diagnosis while in multi-organ failure. Excluding these two, ED was 10/118 (8.5%). The cause of death was disseminated intravascular coagulation(DIC) (n=4), DS (n=2), infection (n=1), multi-organ failure (n=3). Five patients relapsed: 3 were low risk and 2 high risk. There were seven late deaths; relapse (n=2, at 367 and 875 days), second cancer (n=1) and non-APL related comorbidities (n=4).With a median follow-up of 641 (range 1-

1363 days), the 1 year and overall survival (Figure 1) was 88.1% and 85.6%.

Conclusions. Results of our trial using a simplified treatment algorithm along with support from experts and co-management with community physicians decreased induction mortality (8.5%) and improved 1 year survival(88.1%) compared to SEER data (1 year relative survival 71%). Our experience warrants large scale implementation and is presently approved as an ECOG/ACRIN trial (EA9131). This model can be applicable to other cancers and life-threatening diseases.

PO021
RENAL COMPLICATIONS DURING ACUTE PROMYELOCYTIC LEUKEMIA INDUCTION

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Background. Survival rates of patients with APL have increased >90% with the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). However in addition to infections that are common during leukemia induction, bleeding and differentiation syndrome (DS) are frequently seen and are potentially fatal complications unique to APL. Renal failure is considered to be a manifestation of DS but can also occur secondary to infections. Herein, we report development of renal insufficiency (RI) during induction and outcomes in a cohort of patients managed by our program.

Methods. Between 1/2007 and 3/2017, we treated or co-managed a total of 210 patients. Our new group (NG) consists of 138 patients which included, 120 patients treated on a prospective clinical trial in a network of Leukemia treatment centers established in Georgia, South Carolina and neighboring states between July 2013 and May 2016. This program was designed to decrease population wide induction deaths. The other 18 patients were referred to our institution from June 2016 to April 2017 and managed on the same algorithm as the prospective trial. Early Group (EG) consisted of 72 patients between 1/2007 and 5/2013 before initiation of this program. We divided patients into four groups based on the CTCAE v.4.03 classification: Grade I – Creatinine (Cr) rise but less than 1.5 times baseline value; Grade II- Cr greater than 1.5 to 3 times baseline; Grade III- Cr greater than 3 times but less than 6 times baseline and Grade IV - Cr greater than 6 times baseline. Institutional review board approval was obtained and statistics are descriptive.

Results. All patients were treated at our institution in the EG while in the NG 62 (45%) were treated at our institution and 76 (55%) were managed in 33 outlying centers. The median age in EG and NG was 45 years (range 18-86) and 53 (range 19-84) and 61% and 54.3% were females respectively. RI of all grades developed in 29 (40%) in the EG and 32 (23 %) in NG. The breakdown in EG *vs* NG is given in Table 1.

ATRA was the only therapy in 5 (17.2%) vs 5 (15.6%) patients in EG and NG. Other treatment for EG-RI included chemotherapy combined with ATRA in 19 (65.5%), where as in NG-RI only 6 (18.7%) received chemotherapy and ATRA. ATO was combined with ATRA in 4 (13.7%) of EG-RI and 19 (59.3%) of the NG-RI patients. Only 1 (3.4%) patient received ATRA, ATO and chemotherapy in EG-RI and 2 (6.2%) in NG-RI.

Complications among the patients with RI in EG and NG were: DS and infection in 9 (31%) vs 9 (28.1%), DS only in 4 (13.7%) vs 6 (18.7%); infection only in 12 (41.3%) vs 9 (28.1%) respectively. There were 4 (13.7%) vs 8 (25%) in EG and NG which had neither infection nor DS. Among those with DS, steroids were used in 100% of the patients in both EG and NG. There were 11 (37.9%) vs 6 (18.7%) early deaths in patients with renal insufficiency in EG and NG.

Conclusions. By our observation, RI is a frequent complication during induction in APL. Mortality in patients who develop RI tends to be high. Meticulous attention should be paid to kidney function during induction and the drugs should be appropriately dose reduced or held till resolution.

Table 1. Grades of renal insufficiency (RI).

Grades of RI	EG	NG
Grade I	3 (10.3%)	6 (18.7%)
Grade II	14 (48.2%)	17 (53.1%)
Grade III	7 (24.1%)	6 (18.7%)
Grade IV	5 (17.2%)	3 (9.3%)

PO022
WEIGHT GAIN DURING INDUCTION THERAPY OF ACUTE PROMYELOCYTIC LEUKEMIA PATIENTS COULD LEAD TO MAJOR MORBIDITY AND MORTALITY: A PREVENTABLE PROBLEM

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Introduction. Differentiation syndrome can be a major complication of all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO) therapy in acute promyelocytic leukemia (APL) patients. The incidence of DS in studies varies widely and reported between 2-27% mainly due to the definition used for the diagnosis of DS. Dyspnea, unexplained fever, weight gain >5 kg, unexplained hypotension, acute renal failure, and presence of infiltrates and/or pleural, pericardial effusions on chest radiographs are regarded as the signs and symptoms associated with DS. Four or more of these criteria are required for a diagnosis of severe DS but any single criteria is not diagnostic. Weight gain of 5 kg is seen in up to 38% of moderate DS (2-3 criteria) and 68% of severe DS patients. APL patients characteristically have a bleeding tendency at presentation requiring aggressive transfusion support that leads to fluid overload and weight gain unless meticulously monitored. Herein we report our observations with

weight gain in APL patients during induction period.

Methods. Chart review of APL patients managed between 01/2006 and 04/2017 was conducted and patients who gained >5 kg from baseline at admission were identified. Patients from 09/2013 to 04/2017 were managed on an algorithm designed to reduce induction mortality in APL patients and care was provided by physicians dedicated to the management of this disease. The outcomes in these patients was compared to those prior to implementation of the algorithm. The algorithm was a two-page set of guidelines directed at preventing or treating the major causes of early death including meticulous monitoring of the weight as well as aggressive diuresis in the event of weight gain. Institutional review board approval was obtained.

Results. 130 patients were managed during this time period. 57 patients (trial group TG) were managed on the algorithm while 73 (pre-trial, PG) were managed prior to this implementation. Median age was higher in trial patients 48 *vs* 45 years, range being 21-81 in TG vs 19-80 in PG. Median WBC was (4.2 *vs* 2.7) and high risk (WBC > 10,000/mm^3) were higher in the PG vs TG. Median platelet counts were similar. The predominant induction combination was ATRA with chemotherapy in PG (66%) whereas ATRA/Arsenic combination was used in the TG (75%). Median weight gain in the TG was less than PG. (3.15 *vs* 3.5 kg, range 0-12.8 kg vs 0-35 kg). 3 patients in the PG and 1 in the TG did not get treatment and were discharged with comfort care. Excluding these patients, 26 % of patients in TG and 38% in PG gained more than 5kg. The mortality was higher in the PG group at 38% in those that gained more than 5 kg compared to 20% in the TG. In contrast, the mortality was lower in both TG and PG patients with weight gain <5 Kg at 7.1% and 7.4%. Five patients in the PG group did not have follow up weights checked but there was documentation that would satisfy definition of severe DS and all 5 patients died between 4-14 days after admission. The incidence of severe DS was also lower in trial patients (6% *vs* 18%).

Conclusions. Management of APL patients utilizing an algorithm might lead to better monitoring of complications such as weight gain and preventing fluid overload. Meticulous prevention of weight gain during induction could possibly result in a positive outcome. The impact of weight gain on outcomes in comparison to other variables that might impact survival in our cohort will be evaluated further.

PO023
CHRONIC MYELOID LEUKEMIA IN CHILDHOOD: CLINICAL FEATURES AND THERAPEUTIC STRATEGIES BEFORE TYROSINE KINASE INHIBITOR. A SUCCESFUL MEDICAL HISTORY

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Chronic myeloid leukemia (CML) is relatively rare malignancy in childhood; it represents 2–3% of leukemias in pediatric age with an incidence of 0.7 cases/million in patients <14 years and 1.2 cases/million in adolescents (14-20 years). Before the advent of tyrosine kinase inhibitors (TKI), hematopoietic stem cells transplantation (HSCT) was considered the only curative therapy; in adults the milestone therapy was represented by interferon-alfa (IFN), systematically used from 1985 to 2000. In pediatric age, IFN was successfully used, as monotherapy or with cytarabine; results were comparable to adults, as reported by four pediatric retrospective studies. In 1992, in Italy, a network study group for childhood CML was designed with the aim of analyzing diagnostic, biological and clinical features, therapeutic strategies in pediatric centers (AIEOP) and in those dealing with pediatric and adult patients, (AIEOP/GIMEMA) before and after IFN treatment, monitoring approach and follow-up. In the current study, we conducted a retrospective analysis in a 25 years period; 113 patients were enrolled: 38 (34%), from 1978 to 1990 and 75 (66%) in 1991-2002 period; 64 patients in AIEOP and 49 in AIEOP/GIMEMA centers. 36 patients (32%) presented epatosplenomegaly (58%); 102 (90%) were in chronic phase. At diagnosis, 112 patients were submitted to cytogenetic analysis and only 62 performed molecular assessment (18% before 1990 and 78% after 1990, p<0.0001). Both AIEOP and AIEOP/GIMEMA centers employed cytoreductive therapy with hydroxyurea; 83 patients (75%) were submitted to HSCT, with the majority of this procedure (83%) performed in AIEOP centers (p<0.006). 58 patients (51%) received IFN therapy, 65% in AIEOP/GIMEMA versus 41% in AIEOP centres (p<0.023). Duration of IFN treatment was between 1-37 months (median=6 months) in AIEOP centers compared with 2-120 months (median=21 months) in AIEOP/GIMEMA (p<0.0001). At 10 years, overall survival (OS) was 50.8%; 67.5% for patients who performed HSCT alone and 36.6% for those who received IFN followed by HSCT (p=0.0012). OS in patients

treated with IFN, followed by other therapies except for HSCT, was 39.2%. OS was also analyzed by period of diagnosis and age groups (< 10 years old and > 10 years old); no statistical differences were observed (49% *vs* 54.9%; p=0.91 and 56.3% vs 48.1%; p=0.49, respectively). OS was also evaluated by the type of HSCT (sibling, haploidentical and matched unrelated donor); a statistical better outcome was observed in patients submitted to sibling allogenic HSCT (p=0.0004). Heterogeneity in therapeutic strategies, influenced by current clinical practice, emerges from this study: AIEOP centers opted for an approach similar to acute leukemia, while AIEOP/GIMEMA centers used adult CML treatment guidelines of that period. This study led to share management of pediatric CML before TKI advent that has revolutionized prognosis and outcome of CML, avoiding side effects of HSCT and IFN. TKI have been used since 2002 in children and resulted in 100% OS; this is one of the most successful result in pediatric oncohematology.

PO024
HERPES ZOSTER REACTIVATION IN A PATIENT WITH INTERMEDIATE RISK ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH ARSENIC TRIOXIDE AND ALL-TRANS RETINOIC ACID

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Due to the high cure rates of acute promyelocytic leukemia (APL), particularly of low or intermediate risk APL treated with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), management of adverse events (AEs) aiming at reducing morbidity and mortality is becoming increasingly important to further optimize outcome. AEs such as differentiation syndrome (DS), coagulopathy or QTc prolongation are well-recognized and subject of treatment and dosing recommendations. However, besides bacterial and fungal infections in the context of neutropenia, complications due to viral infections in general and particularly varicella zoster virus have not been broadly emphasized so far, although herpes zoster infections have been reported in a larger percentage of patients after treatment with ATO. Here we report on a patient with who was diagnosed with APL and experienced a varicella zoster infection due to reactivation. It was a 75 years old male patient who was transferred to our institution after diagnosis of APL. Blood counts at admission were as follows: WBC 2.810/μL, hemoglobin 9.1 g/dL and platelets 58.000/μL, coagulation parameters were unremarkable besides slightly elevated d-dimers. After 11 days on ATRA and 3 days on ATO he experienced a severe DS with a rapid increase of WBC and lactate dehydrogenase. In addition, acute renal failure and disseminated lung infiltrates were present and the patient was transferred to the intensive care unit. After cessation of ATO and ATRA, initiation of dexamethasone and hydroxyurea and substitution of platelets and coagulation factors the DS resolved and induction treatment with ATRA and ATO could be continued. However, due to QTc prolongation ATO was administered in a reduced dosage during the entire induction therapy. Nevertheless, the patient achieved a complete molecular remission (CR).

After induction treatment, he developed a herpes zoster infection of dermatoma C6. Initial serological testing had shown positivity for IgG but negativity for IgM, while at the time of herpes zoster infection he showed a seroconversion with positivity for IgM, establishing the diagnosis of herpes zoster due to a reactivation of varicella zoster. Antiviral therapy was initiated and the infection completely resolved. Currently at 16 months after completion of the fourth consolidation course, the patient is still in molecular CR. As reported by others, herpes zoster infections can complicate the treatment of patients with APL and clinicians should be aware of them. So far, little is known on the underlying mechanisms, that put APL patients at a higher risk for such infections. Most likely, several factors might contribute to this higher susceptibility such as impaired lymphocytic function, ATO induced apoptosis of lymphocytes and administration of steroids during DS prophylaxis and treatment. However, experimental and clinical studies are warranted to further dissect and identify the main contributors to this complication and to select patients who might benefit from antiviral prophylaxis.

PO025
A UNIQUE PRESENTATION OF DE NOVO ACUTE PROMYELOCYTIC LEUKEMIA AS A MYELOID SARCOMA OF THE BREAST

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Introduction. Myeloid sarcoma (MS) is a presentation of acute leukemia in a various extramedullary sites and appears concomitantly, following or before the onset of systemic bone marrow (BM) leukemia. MS of the breast is extremely rare, with only anecdotal cases seen as isolated before BM infiltration. We describe here, due to our knowledges, the first case of de novo MS of the breast confirmed as acute promyelocytic leukemia (APL).

Case study. A 34-year old woman was presented with 2 month history of painless growing resistance in her left breast. Clinical examination revealed palpable resistances in both breasts with no other clinical symptoms. USG scan, and mammography find tumor lesions which were confirmed by breast magnetic resonance imaging (MRI) showed a 45×24×71 mm tumor mass in the left and 16×12 mm lesion in the right breast. Core cut biopsy set

the diagnosis of MS of APL type after usage of extended panel of immunohistochemical (IHC) markers. Tumor cells were immunoreactive for myeloperoxidase and focally for CD34, Ki-67 index was 60%-70%. The peripheral blood (PB) showed normal parameters of white blood cells 10.2×10^9/L, neutrophils 6.9×10^9/L, hemoglobin 150 g/L, platelets 271×10^9/L. PB film examination showed no abnormal cells and BM aspirate showed trilineage hematopoesis with 3% of blasts and normal cellularity for age. Trephine biopsy was without APL infiltration. Flowcytometry (FC) of BM didn't find any pathological elements. Fluorescent in situ hybridization (FISH) analysis in tissue imprints detected del 7q and the RARA gene rearrangement and additionally molecular analysis using RQ PCR confirm the transcript PML-RARA, bcr3 variant and mutation of ITD FLT3 gene. Karyotype and FISH analysis of PB and BM didn't reported any cytogenetic abnormalities. Molecular analysis confirm the transcript PML-RARA, bcr3 variant, in PB and BM.

Patient was treated according to the Spanish treatment protocol LPA2005. She hadn't neurological symptoms, but because of extramedullary disease lumbar puncture was performed. Cytomorphology of cerebrospinal fluid (CSF) with the atypical promyelocytes and the presence of APL antigen expression on FC confirmed CNS infiltration while MRI of CNS was negative. She continued the protocol for high risk patients and applications of standard intrathecal therapy biweekly for 5 weeks, until CSF negativity. She achieved complete molecular remission in BM after induction. Breast MRI after induction showed residual tumors: 10×23 mm in the left and 4×9 mm in the right breast. She continued with radiotherapy on CNS, TD 24Gy and first consolidation (K1). Complications during pancytopenia after K1 were: pleuropneumonia with partial respiratory insufficiency, mucositis, and severe enterocolitis with paralytic ileus with transitory stay at intensive care unit. Control CT scan revealed abscesses in liver, left kidney and right lung where it formed necrotic abscess with propagation and infiltration of chest wall. These findings limited further treatment plan. Continuation of aggressive CHT was not possible but she refused any other treatment as well. She died of central nervous system failure 5 weeks later in regional hospital.

Conclusions. In the absence of leukemia in BM and PB a diagnosis of MS can be difficult. It should be a routine to send the tissue samples for IHC, FC, FISH and molecular analysis, if the risk of biopsy is reasonable, although all these assays are more difficult to perform on cells in tissue than BM.

PO026
ACUTE PROMYELOCITIC LEUKEMIA IN THE THIRD TRIMESTER OF PREGNANCY: TWO DIFFERENT APPROACHES

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Acute promyelocytic leukemia (APL) is an uncommon leukemia with excellent prognosis thanks to all-trans retinoic acid (ATRA) treatment based. However, APL presenting during pregnancy is consider an infrequent and challenging entity as the evidence-based information available in this setting is limited with most published data based in small series or case reports. Front-line treatment of APL with AIDA-regimen (ATRA plus Idarubicin) has been the standard of care in our country (Spain) until the recent approval of arsenic trioxide (ATO). Besides, ATO is potentially embryotoxic in humans and it is not currently recommended in any stage of pregnancy.

We report our experience in treating two pregnant women diagnosed with APL in the third trimester from two different approaches: treating with AIDA-regimen to the pregnant woman when APL is diagnosed in the early third trimester versus delivery induction within the late third trimester.

In the first case, a 40-year-old female at 27-week gestation was diagnosed with APL after recurrent episodes of hematuria and pancytopenia. Patient had no previous comorbidities or complications until that moment despite of in vitro fertilization (IVF). She was diagnosed with intermediate risk APL (39×10^9/L platelets and 1.55×10^9/L leukocytes) with coagulopathy and, after reviewing the scientific evidence and discussing the case in a multidisciplinary team including gynecologists and neonatologist, she was treated according to PETHEMA LPA2012 protocol with ATRA and Idarubicin. The fetus was exhaustively monitored by echocardiography showing only mild oligoamnios without any cardiac disfunction which was our main concern due to anthracyclines potential toxicity. Treatment was well tolerated until day 31 when she developed hypertension so a cesarean section was performed. Preterm male child with a birth weight of 1,45 kg was born. Baby had normal blood counts but suffered from broncho-pulmonary dysplasia. As IVF is strongly associated with pre-eclampsia and cesarian section and broncho-pulmonary dysplasia is present up to 0,84% in preterm infants, wether treatment given to the mother during pregnancy played a role in these complications or not remain unclear. The mother continued ATRA therapy after delivery and is currently in complete remission (CR) at day 76. The second case was a 32-year-old female at 33-week gestation diagnosed with intermediate risk APL (2×10^9/L platelets and 1.17×10^9/L leukocytes) with coagulopathy after gingival and cutaneous bleeding. She developed severe respiratory failure requiring tracheal intubation in the first 24h after diagnosis without receiving any specific treatment for APL. Considering mother condition and gestational age, a cesarian section was performed and a healthy female with a

birth weight of 2,1kg was born without neither perinatal nor late complications. Patient received then AIDA-regimen according to PETHEMA LPA2005 protocol achieving CR and is alive after 8 years of follow-up.

Conclusions. In our experience, AIDA-regimen is effective and relatively safe in the third trimester for the mother. Regarding to the fetus, risk-benefit should be well balanced to decide wether a premature birth not being exposed to ATRA and Idarubicin is preferable to delaying the delivery and facing potential toxicities. Induction delivery in late third trimester could be also an appropriate option.

PO027
DIFFERENCE IN CAUSES AND PROGNOSTIC FACTORS FOR EARLY DEATH BETWEEN COHORTS WITH *DE NOVO* AND RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA

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Background. Early death (ED), either before treatment is initiated or within the first 30 days of induction treatment, remains the most critical issues in the current care of patients with acute promyelocytic leukemia (APL). Information on ED has been reported repeatedly in the *de novo* patients, whereas few studies have focused on relapsed patients. In this retrospective study, the difference in baseline clinical features, rate, causes and prognostic factors of ED was compared between cohorts with relapsed and *de novo* APL.

Methods. Totally 285 new and 79 hematologically relapsed patients were included. They were all treated in The First and The Fourth Affiliated Hospitals of Harbin Medical University, and received arsenic trioxide alone as induction therapy. Eleven clinical parameters were chosen for analysis, including age, sex, fever, white blood cell (WBC) and platelet account, serum fibrinogen, D-dimer, creatinine, uric acid, albumin and aspartate aminotransferase levels. All continuous variables were dichotomized and the cutoff points were set at the threshold between normal and abnormal levels or based on published studies. Univariate and multivariate analyses were performed using Pearsons Chi-square test or Fisher's exact test and logistic regression model with backward stepwise selection of variables. Risk factors for ED were evaluated in 3 cohorts, *i.e*. the all patient cohort, the *de novo* cohort and the relapse cohort. For the all patient cohort, the predictive significance of *de novo*/relapse classification was also evaluated in both the univariate and multivariate analyses to study if relapse is associated with ED, and the predictive significance of interaction of *de novo*/relapse classification with other 11 variables was also evaluated in the multivariate analysis to study if odds ratios of risk factor for ED were homogenous between the *de novo* and relapse cohorts after adjustment for other risk factors.

Results. Compared with the *de novo* patients, the relapsed patients had significantly less fever, lower WBC count and D-dimer level and higher platelet count, serum fibrinogen and albumin levels (all $P<0.05$), revealing that upon hospital admission the overall condition of the relapsed patients appeared relatively superior to that of the new patients. The ED rate in the relapse cohort (19, 24.1%) was somewhat higher than that in the *de novo* cohort (51, 17.9%), although the difference is not significant ($p=0.219$). For both cohorts, hemorrhage was the main cause of ED (37 *de novo* versus 14 relapsed patients), followed by differentiation syndrome (12 new versus 2 relapsed patients), infection (8 new versus 2 relapsed patients) and other causes. Relapse was not independent predictor for ED, whereas interaction of *de novo*/relapse classification with uric acid level was independently associated with ED in the all patient cohort. Increased creatinine level, older age, male sex, WBC count$>10\times10^9$/L and fibrinogen<1 g/L were independently associated with ED in the new patients. While WBC count$>10\times10^9$/L, elevated uric acid level and D-dimer>4 mg/L were independent risk factors for ED in the relapsed patients.

Conclusions. This is the first report that provides useful information on ED in patients with relapsed APL. These data furnish clinically relevant information that might be useful for designing more appropriately risk-adapted treatment protocols aimed at reducing ED rate in relapsed patients.

PO027bis
REAL LIFE EXPERIENCE WITH ATRA-ARSENIC TRIOXIDE BASED REGIMEN IN ACUTE PROMYELOCYTIC LEUKEMIA – UPDATED RESULTS OF THE PROSPECTIVE GERMAN INTERGROUP NAPOLEON-REGISTRY

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Background. Standard therapy of acute promyelocytic leukemia (APL) has long relied on the combination of All-trans-retinoic acid (ATRA) and chemotherapy. The introduction of arsenic trioxide (ATO) into APL treatment resulted in similarly high remission and survival rates coupled with significantly reduced myelosuppression. Recent results of the APL0406 trial by the GIMEMA-AMLSG-SAL study groups showed that the combination of ATRA and ATO is superior to standard ATRA and chemotherapy (CHT) in front-line therapy of low/intermediate-risk APL. The implications of these results for the clinical practice of APL patients in Germany have been uncertain given the fact that ATO has only recently been licensed for front-line therapy in APL subgroups.

Aim. In order to provide a picture of the clinical reality of APL patient care in Germany an intergroup APL registry (National acute promyelocytic leukemia (APL) observational study, NAPOLEON) was recently initiated by 4 AML study groups.

Table 1: Selected demographic, clinical and laboratory characteristics of the 77 eligible patients treated by ATRA-ATO regimen.

	ATRA-ATO (n=77)
Median age, years (range)	52 (20 - 87)
Median WBC, 10^9/L (range)	2.2 (0.3 – 10)
Sanz risk	
Low/intermediate, n (%)	77 (100)
FLT3-ITD, n mutated / n total (%)	6/48 (13)

Methods. Eligible patients are adults at least 18 years of age with newly diagnosed or relapsed APL within the first year after diagnosis. Here we report the analysis on the series of patients prospectively enrolled into this registry. The study was conducted in accordance with the Declaration of Helsinki, received IRB approval by all participating centers and was registered at ClinicalTrials.gov (NCT02192619).

Results. As of August 1st 2017, 150 patients (median age 54 years; range 19-87) with newly diagnosed APL have been included into the study. Among all patients 67% (n=100) were low/intermediate-risk according to the Sanz score. Out of these patients 77% (n=77) received an ATO-ATRA based induction regimen followed by a median of 4 courses of ATO-ATRA consolidation (according to the APL 0406 study). Of 76 patients treated by ATRA-ATO regimen that were evaluable for response to induction, 75 (99%) patients achieved a complete remission (CR). One patient died within 30 days of therapy resulting in an early death rate of 1%. After a median follow-up of 14 months, event-free survival, cumulative incidence of relapse and overall survival at 12 months for these patients were 97%, 2% and 97%, respectively. The therapy was well tolerated and no new safety signals have been obtained.

Conclusion: These real life data from a prospective German registry provide further evidence for the safety and sustained anti-leukemic efficacy of ATRA-ATO in low/intermediate-risk APL. These results further support ATRA-ATO as the new standard of care in this clinical setting.

PO028
CLINICAL IMPACT OF BAALC EXPRESSION IN HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA

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Although BAALC overexpression is associated with primary resistant disease, shorter relapse-free, disease-free, and overall survival in different subsets of acute myeloid leukemia (AML), little is known about its clinical impact in acute promyelocytic leukemia (APL). Using real-time reverse transcriptase polymerase chain reaction, we showed that BAALC expression is significantly lower in APL compared to other subsets of AML ($p<0.001$). We also demonstrated that BAALC overexpression was associated with shorter disease-free survival (hazard ratio, HR: 4.43, 95% confidence interval, CI: 1.29–15.2; P=0.018) in 221 consecutive patients (median age: 35 years, range: 18–82 years) with newly diagnosed APL homogeneously treated with all-trans retinoic acid and anthracycline-based chemotherapy. Cox proportional hazard modeling showed that BAALC overexpression was independently associated with shorter disease-free survival in the total cohort (HR: 5.26, 95% CI: 1.52–18.2; p=0.009) and in patients with high-risk disease (i.e. those with initial leukocyte counts $>10\times10^9$/L) (HR: 5.3, 95% CI: 1.14–24.5; P=0.033). Although initial leukocyte and platelet counts are currently used as markers to predict relapse in APL, these parameters can change significantly in a short period of time. Based on our experience and on the experiences of others, the use of genetic data could improve risk stratification in APL. This could help clinicians make decisions about consolidation strategies and also provide the possibility of early intervention if molecular relapse occurs. However, the findings of all of these studies should be interpreted with caution, since most of them, including our own, lack validation in an independent cohorts and are limited by their sample sizes. Furthermore, we cannot rule out the possibility that methodological differences between studies could lead to different results and conclusions. More importantly, it is very likely that all of the molecular markers described so far will not remain clinically valid if the all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) regimen become the most used protocol worldwide. Meanwhile, alternative strategies for improving prognostication in APL should be tested, particularly in countries in which the clinical use of arsenic has not yet been authorized. We conclude that BAALC expression could be useful for refining risk stratification in APL, although this needs to be confirmed in independent cohorts.

PO029
REDUCTION OF HOSPITALIZATION AND TRANSFUSIONAL SUPPORT WITH FIRST LINE ARSENIC TRIOXIDE IN COMBINATION WITH ALL-TRANS RETINOIC ACID COMPARED TO CHEMOTHERAPY IN COMBINATION WITH ALL-TRANS RETINOIC ACID IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA: MONOCENTRIC EXPERIENCE

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Introduction. Acute promyelocytic leukemia (APL) is characterized by the translocation t(15;17), which generates an abnormal fusion protein, PML-RARα. The discovery of the molecular pathogenesis has led to the first targeted therapy for acute leukemia: the retinoic acid. The major component of therapy is all-trans retinoic acid (ATRA), usually associated to anthracycline-based chemotherapy. It obtained high response rates but some potential long-term sequelae are described. The introduction of acid trioxide (ATO) tried to obviate such complications. We noted that this treatment allowed patients (pts) to be recovered only during the induction phase and in case of complications and also the transfusional support seemed to be reduced. The aim of the study was the analysis of our experience of APL pts treated with ATO plus ATRA compared to pts treated with chemotherapy plus ATRA in terms of days of hospitalization and number of transfusions.

Description. From January 2009 we treated 12 APL pts with ATO plus ATRA regimen according to GIMEMA

protocol APL0406 (Platzbecker U, J Clin Oncol. 2016). Their characteristics are summarized in Table 1 together those of the control cohort treated with chemotherapy plus ATRA according to AIDA-2000 (Lo Coco F, Blood 2010). All pts started ATRA immediately and they were admitted to the hospital for the induction phase. The median time of the first recovery was in first arm 34 days (range 28-47) and in the second arm 31 days (range 25-46). During this phase there was the major transfusional support: in the first arm the mean number of units of red blood cells (RBC), platelets and fresh frozen plasma (FFP) was 4.5, 7 and 3 respectively, on the contrary in the second arm it was 4, 6 and 10 respectively. All but 1 pt followed the consolidation phase as outpatients, no complications which needed hospitalization were registered except 1 pt admitted for the suspect of benign endocranial hypertension. No one has been supported by transfusion. In the second arm all the pts followed the consolidations as inpatients: for the first consolidation the median time of recovery was 6 days (range 5-7) and all but 2 pts needed a second admission for neutropenia and other complications of 9 days (range 7-15); during it 3 pts were supported with RBC and platelets. Regarding the second consolidation all the pts experienced a first recovery of 7 days (range 6-9) followed by a second admission of 11 days (range 8-18); 8 pts needed platelets and 6 pts RBC. Only 2 pts were admitted to the hospital for the third consolidation but 5 pts required hospitalizations for complications and 1 platelets transfusion.

Discussion. ATO plus ATRA regimen shows a series of advantages allowing to treat pts in which chemotherapy could not be the first choice or it could even not be applicable. Considering our analysis this approach allowed also to reduce hospitalization and transfusional support: all pts of the second arm required platelets, RBC and FFP with a major load of FFP in confront of the first arm. No one of the first arm required elective admission for the therapy and also admissions for complications was extraordinary; the number of admissions for the pts of the second arm was consistent both for first and second consolidation phase and the transfusional support was significant.

Conclusions. The association of ATO to ATRA is not only an efficacious chemo-free regimen but it seems to reduce cost in terms of hospitalization and transfusional support.

Table 1 Patients' characteristics.

		First arm (ATO plus ATRA) 12 pts	Second arm (Chemiotherapy plus ATRA) 12 pts
Median age (years)		45.5 (range 24-62)	42 (17-60)
Gender M/F [ratio]		9/3	7/5
WBC count (mmc)		1070 (range 650-9770),	3350 (range 800-117000)
Hemoglobin (g/dl)		9.1 (range 6.1-12.8)	9.9 (range 5.3-14.5)
Platelets count (mmc)		25.5 (range 9-136)	23 (range 7-119).
Risk category	High	0	4
	Intermediate	9	6
	Low	3	2

PO030
OLDER METHODS AND (NEW) DRUGS: A CASE REPORT OF ACUTE PROMYELOCYTIC LEUKEMIA

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A 40 yeard old patient consulted his general practitioner because of a non-improving cold.

Blood test analysis revealed a bicytopenia marked by a leucopenia with deep neutropenia and monocytopenia: hemoglobin level was 13.1 g/dL, hematocrit 38.3% and neutrophils and monocytes count was 560 and 20 cells per microliter, respectively. The coagulation tests were normal. He was referred to our university hospital where a blood marrow aspiration showed a predominance of hypergranular promyelocytes and the presence of faggot cells. Immunophenotyping by flow cytometry showed a large blast population negative for CD34, HLA-DR, CD15 and positive for CD117, CD33 (strong homogenous positivity) and MPO. Immunofluorescence staining with an FITC-labeled anti-PML antibody showed a characteristic nuclear microgranular pattern which confirmed the diagnosis of ATRA-sensitive acute promyelocytic leukemia. Cytogenetics certified this diagnosis with the typical t(15;17) translocation.

He was started on all-trans-retinoic-acid (ATRA) at 45 mg/m once a day and arsenic trioxide at 0.15 mg/kg daily. On fifth day of treatment neutrophils count fell below 500/μL whereas red blood cells and platelets count remained normal during the entire treatment. One week after the induction treatment ATRA-induced scrotal ulcers appeared. On day 40 after the start of the induction treatment a second bone marrow analysis showed a diffuse and pronounced dyserythropoiesis associated with an important granulocytic hypoplasia, consistent with arsenic toxicity. No blasts were put into evidence. On day 60 there was still no sign of hematological recovery. The treatment was discontinued and a third bone marrow aspiration was performed but the results confirmed the hallmarks of arsenic toxicity and the absence of blasts. On day 68 the patient was discharged with neutrophil and monocyte count of 210 and 270 cells/μL, respectively. On day 75, when he was reevaluated at our outpatient clinic, the CBC confirmed complete hematological recovery, with a neutrophil and monocyte count of 1.101 and 470 cells per microliter, respectively.

During all hospital stay no complication was observed, except scrotal ulcers on ATRA.

The median duration of aplasia in the protocol we followed is much shorter than observed in our case (median of 33 versus 72 days) but recovery was rapid after treatment discontinuation.

In the setting of an APL it is crucial to start promptly the appropriate chemotherapeutic regimen. Our laboratory could confirm the diagnosis on the basis of the presence of hypergranular promyelocytes displaying evidences of cytological anarchy. An important element for the diagnosis of APL was the dispersion of the nuclear PML bodies observed by immunofluorescence, reflecting the PML-RARalpha translocation. This finding allows a

rapid cytological diagnosis of APL even in the presence of cryptic translocation of PML/RARalpha , which could sometimes be misdiagnosed by molecular techniques.

PO031
APL IN OBESE: SHOULD WE TREAT IT DIFFERENTLY?

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We have been using GIMEMA protocol with All-trans retinoic acid (ATRA)/Arsenic trioxide (ATO) in treating low and intermediate risk APL for the last 2 years. Surprisingly, the two most difficult cases to manage during induction had a body mass index (BMI) of > 30, compared to the 16 cases with BMI< 30, during the same period.

A summary of the 18 newly diagnosed low and intermediate risk patients treated by us in the last 2 years is presented below:

Category	Obese (BMI >30) n=2	Non-obese (BMI<30) n=16
Age range (years)	25-52	11-26
Mean (years)	38.5	18.5
Gender;		
Male (n=9)	01 (50%)	08 (50%)
Female (n=9)	01 (50%)	08 (50%)
Mean BMI (kg/m^2)	31.5	22.4
Development of differentiation syndrome (DS)	02 (100%	07 (43.75%)
Days of onset of DS after initiation of induction	9	11
Mean duration of DS (days)	11.5	4
Differentiation syndrome related mortality	02 (100%)	00 (0%)
Mortality due to fungal pneumonia	00 (0%)	01 (6.25%)
Mortality due to bleeds	00 (0%)	00 (0%)
Overall induction mortality	02 (100%)	01 (6.25%)

We reviewed the literature and found that majority of the cases of APL in western countries were either overweight or obese with a median BMI of >30, in patients treated with the same protocol. We also found that high BMI was an independent predictor of differentiation syndrome, which was mostly severe or fatal. Though the number of cases is small, we believe that possibly obesity makes things more difficult to manage and obese with low or intermediate risk APL should perhaps be treated in a different manner especially during induction.

PO032
IS ARSENIC TRIOXIDE (ATO) REQUIRED IN THE TREATMENT OF HIGH RISK NEWLY DIAGNOSED APL? ANALYSIS OF A RANDOMIZED TRIAL (APL2006) BY THE FRENCH BELGIAN SWISS APL GROUP

Ades L, Raffoux E, Spertini O, Guerci A, Récher C, Guyotat D, Deconinck E, De La Chapelle TL, Thomas X, Bordessoule D, Vey N, de Botton S, Pigneux A, Caillot D, Cahn J-Y, Chevallier P, Lambert J-F, Gardin C, Dombret H, Lejeune J, Chevret S, Fenaux P

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Background. In standard risk APL, ATRA+ATO combinations (without CT) are at least as effective as classical ATRA + anthracycline based chemotherapy (CT) while being less myelosuppressive (Lo Coco 2014, Burnett 2015). In high risk APL (WBC> 10G/l), it is still unclear if CT can be avoided or greatly reduced, but addition of ATO to ATRA + CT reduces relapses (Powell, Blood 2010). In a randomized trial (APL2006 trial) in high-risk APL patients who received ATRA + CT induction treatment, we evaluated the addition of ATO to CT during consolidation.

Methods. Between 2006 and 2015, newly diagnosed APL pts <70 years with WBC> 10 G/L, after an induction of ATRA 45 mg/m^2/d until CR with Idarubicin (Ida) 12 mg/m^2/dx3 and AraC 200 mg/m^2/dx7, were randomized for consolidation between CT and CT+ATO. The CT group(standard group) received a first consolidation with Ida 12 mg/m^2/dx3 and AraC 200 mg/m^2/dx7, a second consolidation with Ida 9 mg/m^2/dx3 and AraC 1g/m^2/12h x4d, and 2-year maintenance with intermittent ATRA and continuous 6 MP + MTX. The CT+ATO group received the same treatment except that ATO 0.15 mg/Kg/d d1 -25 was added during both consolidation courses. After a first interim analysis in Sept 2010, based on 81 pts, AraC was deleted from consolidation cycles of the CT+ ATO group. The primary endpoint was EFS from CR.

Results. 211 pts <70 years with WBC> 10 G/L were included (after the exclusion of 8 diagnostic errors) in 58 centers. 95.7% achieved CR, 3.3% had early death and 1% resistant leukemia. 193 pts were randomized for consolidation, 97 in the CT and 96 the CT+ ATO groups. Pretreatment characteristics were well balanced between the 2 groups. 7 pts (3 CT *vs* 4 CT+ATO) had relapsed (5-year CIR of 2.5% vs 3.9%; p=0.39) and 9 pts had died in CR :7 (7.8%), 2 (5.1%), 0 (0%) in the CT, CT (with AraC) + ATO, CT (without AraC) + ATO groups respectively (p=0.04). Causes of death in CR were bleeding (n=5), infection (n=2), previous cancer relapse (n=2). One patient in the CT+ATO arm developed AML/MDS.

5-year OS was 93% *vs* 94% (p=0.56) and 5-year EFS was 89% *vs* 93% (p=0.47) in the CT and CT+ATO groups, respectively. Omission of AraC (after the amendment) in the CT+ATO group did not increase CIR (5 year CIR 5.3% with and 3.3% without AraC, p=0.57). In the CT, CT (with AraC) + ATO, CT (without AraC) + ATO groups respectively, median time to ANC>1 G/L after consolidation 2 was 22, 25 and 19 days (p<0.0001), and median time to platelets>50G/l was 24, 26 and 20 days

(p<0.0001). Similarly, median duration of hospitalization after the first and the second consolidation courses were 33, 34, 29 d (p<0.0001) and 31, 32, 28 d (p=0.0005), respectively.

Conclusions. Very high CR rates and very few relapses are now obtained in high risk APL on a large multicenter basis using classical ATRA and CT (including AraC) for induction and consolidation, and maintenance treatment, but at the expense of 5 to 7% deaths in CR. Addition of ATO to this regimen did not further reduce relapses, and added some myelosuppression if CT contained AraC. However, if ATO was added and AraC omitted from consolidation cycles, relapses were not increased, while myelosuppression and deaths in CR were reduced. ATO therefore appears useful in high risk APL. We are currently comparing, in the international APOLLO trial, the *classical* ATRA-CT approach and a ATO-ATRA regimen with only 2 days of Ida during induction treatment, hoping to further reduce myelosuppression and possibly relapses.

PO033
IS ARSENIC TRIOXIDE (ATO) REQUIRED IN THE TREATMENT OF STANDARD RISK NEWLY DIAGNOSED APL? ANALYSIS OF A RANDOMIZED TRIAL (APL 2006) BY THE FRENCH BELGIAN SWISS APL GROUP

Ades L, Thomas X, Guerci-Bresler A, Emmanuel R, Spertini O, Vey N, Lamy T, Récher C, Pigneux A, Bordessoule D, Deconinck E, Gardin C, Tournilhac O, Lambert J-L, Chevallier P, de Botton S, Lejeune J, Dombret H, Chevret S, Fenaux P

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Background. ATO is very effective in the treatment of APL and recent results have shown that ATRA+ATO combinations (without CT) were at least as effective as classical ATRA + anthracycline based chemotherapy (CT) while being less myelosuppressive (Lo Coco 2014, Burnett 2015). In a randomized trial (APL 2006 trial), we compared for consolidation treatment (after ATRA CT induction treatment) ATO, ATRA and the *classical* Ara C in standard risk APL (ie with baseline WBC < 10G/L).

M*ethods*. Between 2006 and 2013 newly diagnosed APL patients (pts) <70 years with WBC < 10 G/L , after an induction treatment consisting of ATRA 45 mg/m^2/d until CR with Idarubicin (Ida) 12 mg/m^2/dx3 and AraC 200mg/m^2/dx7 started on day 3, were randomized for consolidation between AraC, ATO and ATRA. The AraC group (tandard group) received a first consolidation course with Ida 12 mg/m^2/dx3 and AraC 200 mg/m^2/dx7, a second consolidation with Ida 9 mg/m^2/dx3 and AraC 1 g/m^2/12h x4d, and a maintenance during two years with ATRA 15d/ 3 months and continuous 6 MP + MTX. The ATO and ATRA groups received the same treatment as the AraC group, but AraC was replaced respectively by ATO 0.15 mg/Kg/d d1 to 25 and ATRA 45 mg/m^2/d d1 to 15 for both consolidation courses.

Results. Among the 398 included pts, 7 were excluded for diagnosis error, 96% achieved CR, 12 (3%) had early death (from bleeding (n=1), sepsis (n=6), Thrombosis (n=4), cardiac arrest (n=1) and 4 (1%) had resistant leukemia. 353 pts were randomized for consolidation. Pretreatment characteristics were well balanced between the 3 consolidation groups. Overall, 4, 0, and 7 pts had relapsed (p=.03) and 6, 5, and 5 pts (p=.93) had died in CR in the AraC, ATO and ATRA consolidation groups, respectively. Causes of death in CR were sepsis (n=4) and hemorrhage (n=2), AML/MDS (n=5), relapse of a previous cancer (n=2), other (n=2). Two of the 6 deaths in CR related to myelosuppression occurred in each arm. Of the 5 patients who developed AML/MDS, 2, 1 and 2 had been treated in the AraC, ATO and ATRA arms, respectively. Five-year EFS from randomization was 90.8%, 92.5% and 86.8% (p=.52), 5y CIR was 3.89%, 0%, 7.41%(p=.03) and 5 year OS was 93.6%, 92.8% and 91.9% (p=NS), in the AraC, ATO and ATRA consolidation groups, respectively. Median time to ANC >1 G/L after the first consolidation course was 24, 24 and 17 in the AraC, ATO and ATRA group, respectively (AraC vs ATO: p= .96; ATO vs ATRA: p<.0001). Similarly, time to ANC >1 G/L after the second consolidation course was 23, 19 and 13 days (AraC vs ATO: p= .02; ATO vs ATRA: p <.0001). Median duration of hospitalization after the first and the second consolidation course were 32d, 29d, 32d (p= NS) and 30d, 17d, 15d in the AraC, ATO and ATRA group, respectively (p<.0001).

Conclusions. Very high CR rates are now obtained in standard risk APL on a very large multicenter basis using classical ATRA and anthracycline based CT combinations, with very few relapses. On the other hand, our results strongly suggest that relapse rates observed with regimens without ATO, although they are low, can be significantly further reduced by addition of ATO. The Ida-ATRA consolidation regimen in particular, while carrying reduced toxicity, was associated with a relapse rate of 7.4%. Our results therefore advocate systematic introduction of ATO in the first line treatment of standard risk APL, but probably not concomitantly with CT, a situation where we found myelosuppression to be significant.

PO034
DIFFERENTIATION SYNDROME IN ACUTE PROMYELOCYTIC LEUKEMIA: A MONO CENTRIC STUDY

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Introduction. Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia(AML) , it's relatively rare form of leukemia, accounting for about 10-15% .The disease is identified by distinctive morphology and by a balanced reciprocal translocation between chromosomes 15 and 17; resulting in a fusion of PML(promyelocytic leukemia) and RARA (retinoic acid receptor alpha) genes.This defect can specifically be overcome by pharmacologic amounts of the retinoid all-

trans retinoic acid (ATRA).

The introduction of all-trans retinoic acid (ATRA) into therapy of APL completely revolutionized the management and the pronosis of this disease.

Howether ATRA is responsible of a differentiation syndrome (DS), which is a life threatening complication characterized by respiratory distress, unexplained fever, weight gain, and interstitial lung infiltrates, pleural or pericardial effusions, hypotension and acute renal failure.

Patients and methods. It is a retrospective study of descriptive type carried out over a period of 3 years from January 2014 to December 2016, concerning all cases of LAP were listed. The diagnosis is made by the morphological study of blood and medullary smear according to FAB classification, and immunophenotypic in some cases but no cytogenetic study could be performed. From a therapeutic point of view, patients received ATRA (combined with chemotherapy) in induction during consolidation and maintenance therapy. We evaluate the side effect of ATRA and particularly of differentiation syndrome.

Results. During the study period, 13 cases of LAP were diagnosed, 12 adults and one child, the median age was 27.5 years (13 to 46 years), the sex ratio was 0.35 (5 H / 9 F). According to the prognostic score of Sanz, 6 patients (46.1%) are of high risk, 5 patients (38.4%) are intermediate risk and 2 (15.3%) low risk. ATRA was initiated upon diagnosis suspicion, all patients received corticosteroids as preventive, dexamethasone in 9 patients and prednisolone in 4 patients. DS was observed in 6 patients (46.1%). The median time to onset is 13 days (2 to 33 days), 4 patients have a high score of Sanz (66.6%). The GB rate at diagnosis is > 5G / L in 5 patients (83%).

Respiratory disorders, mainly effusions and dyspnea, were reported in 3 patients (23%). Signs of retention (edema, weight gain, effusion) were observed in 6 patients (46.1%),no renal or hepatic impairment was reported. Other side effects of ATRA have been observed, psychiatric disorders in 2 patients and myositis in one patient.ATRA was discontinued in 4 patients (66.6%).

Conclusions. DS is an unpredictable complication of ATRA's treatment of APL, occurs generally after a few days or weeks of initiation of treatment. Its incidence in our series remains greater than that of the literature (20-25%).

Treatment involves the administration of intravenous steroids for a period of days or weeks after clinical resolution. In severe cases (acute renal or respiratory failure) it seems reasonable to interrupt ATRA until clinical recovery.

PO035
THE KINETICS OF WHITE BLOOD CELL AND PREDICTIVE FACTORS OF LEUKOCYTOSIS UNDER THE ORAL ARSENIC OR INTRAVENOUS ARSENIC AS FIRST-LINE TREATMENT FOR ACUTE PROMYELOCYTIC LEUKEMIA

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Objective. We aimed to compare the kinetics of white blood cell and explore predictive factors of leukocytosis in non-high-risk acute promyelocytic leukemia (APL), with oral arsenic plus all-trans retinoic acid (ATRA) or intravenous arsenic trioxide (ATO) plus ATRA as frontline treatment.

Methods. The absolute count, doubling time and peak time of white blood cell (WBC) were comparably analyzed among 64 newly diagnosed non-high-risk APL patients treated by different induction regimen with oral realgar-indigo naturalis formula (RIF) (n=35) or with ATO (n=29) involved in our APL07 study. The end points were the dynamic changes of WBC count during induction. The analyzing time points were respectively set from day 1 begin, after the interval of 3 days.

Results. Among 64 patients, the median WBC count at presentation and peak were 1.78 (range 0.31-9.89)$\times 10^9$/L and 12.16 (range 1.56-80.01)$\times 10^9$/L. The incidence of differentiation syndrome (DS) was 9.38%. The dynamic changes of leukocytosis shown a single peak wave in all patients and the median time to peak was 10(range 2-26) days. A higher WBC count was observed in RIF group compared with ATO group at 10 days treatment (9.22 $\times 10^9$/L vs. 4.10$\times 10^9$/L, p=0.015). Patients with the peak WBC count > 10×10^9/L had shorter doubling time of WBC compared with others (RIF group 4 days vs. 7days, p=0.001; ATO group 4.5 days vs. 23days, p=0.002). Univariable and multivariable analysis showed that the doubling time of WBC is an independent factor for the peak WBC count.

Conclusions. Different kinetics of WBC was shown during induction with oral arsenic plus ATRA and ATO plus ATRA. The doubling time of WBC is an important, independent factor for the peak WBC count.

PO036
CHARACTERISTICS AND CLINICAL OUTCOME OF APL PATIENTS FROM THREE DIFFERENT COUNTRIES TREATED WITH THE PETHEMA LPA2005 PROTOCOL

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Background. The preliminary analysis of the PETHEMA LPA2005 trial showed improved results by the addition of cytarabine to the consolidation schedule in high-risk patients, as well as a slight dose deintensification in older patients. However, the reproducibility of these results between different participating countries has not been assessed.

Objectives. In this study we aim to analyze the disease and patient´s characteristics, as well as the main clinical outcomes of three cooperative groups form Poland (PALG), the Netherlands (HOVON), and Spain (PETHEMA) who participated in the LPA2005 trial.

Materials and Methods. Between 2005 and 2013, 740 consecutive patients were enrolled in the LPA2005 trial. Treatment consisted of Induction therapy with oral ATRA (45 mg/m^2/d) and intravenous idarubicin (12 mg/m^2/d x4 days) followed by three courses of consolidation with ATRA and chemotherapy. Maintenance therapy consisted of intermittent ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurine. Main exclusion criteria were ECOG 4, contraindication for chemotherapy, and secondary APL.

Results. Overall, 580 patients (79%) were from PETHEMA, 84 (11%) from HOVON, and 76 (10%) from PALG. No significant differences were observed regarding the relapse-risk classification (high-risk in 28%, 25%, and 25% in the PETHEMA, PALG, and HOVON, respectively). The main observed differences between PETHEMA, PALG, and HOVON patients were: median age (43 *vs* 38 vs 45 years, respectively, p=.05), ECOG<2 (80% *vs* 68% vs 87%, respectively, p<.001), fever at presentation (34% vs 26% vs 17%, respectively, p=.008), fibrinogen levels <170 mg/dL (43% *vs* 52% vs 59%, respectively, p=.002), variant M3 morphology (19% vs 6% vs 6%, respectively, p<.001), and LDH levels >600 UI/L (37 *vs* 29 vs 17, respectively, p=.002). The complete remission rate was similar between the three groups (92% vs 91% *vs* 94% (p=0.73). The estimated CIR at 5 years was 11% in PETHEMA, 8% in PALG, and 13% in HOVON patients (p=0.69). The estimated OS and EFS at 5 years was 85% and 78% in PETHEMA, 87% and 82% in PALG, and 86% and 78% in HOVON patients (p=.53 and p=.71).

Conclusions: Our study shows the reproducibility of the PETHEMA LPA2005 trial results between three different European countries.

PO037
EXPERIENCE WITH ATO AND ATRA TREATMENT IN PEDIATRIC PATIENTS WITH LOW RISK APL

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Studies in adults with acute promyelocytic leukemia (APL) showed high cure rates in low-risk patients treated with all-trans retinoid acid (ATRA) and arsenic trioxide (ATO), while toxicities were significantly reduced compared to the standard treatment with ATRA and chemotherapy.[1] First experience of the AML-Berlin-Frankfurt-Münster (BFM) consortium with an ATRA-ATO therapy schedule are presented focussing on toxicities.[2]

There were 13 patients with low-risk APL aged 1 to 17 years, who were treated in 9 different hospitals in Germany and Austria since 2013 with the ATRA-ATO regimen, which resembled the Lo Coco regimen for adults.[1] Differences to the original scheme were: A later start of ATO (0.15 mg/kg/day i.v. 1-2 hour infusion) on day 10 (this was done to avoid hyperleukocytosis burst due to simultaneous ATO/ATRA at onset); a one week break of ATRA (25 mg/m /day) application after the first 14 days, seven intrathecal therapies with cytarabine (in age-dependent dose) every 4 weeks starting at day 10 (after blast cell reduction). In case of increasing WBC count (hyperleukocytosis > 10,000/μL) low dose cytarabine and/or hydroxyurea was recommended. Two patients received chemotherapy induction because therapy started in a hospital not involved in the consortium or the case was initially misdiagnosed as AML FAB M2.

All patients achieved molecular remission after 7 – 20 weeks (median 10 weeks) and have remained in remission until now (follow-up 1.0 – 3.8, median 2.4 years). Those 11 patients, who got no initial chemotherapy, suffered from hyperleukocytosis (WBC >10,000/μL) during the first 4 weeks. The peak of WBC values was on day 14 of treatment. In 6 of them hyperleukocytosis with clinical signs of differentiation syndrome occurred, in 4 of them this happened after starting ATO treatment. Along with hyperleukocytosis, one patient suffered from painful spotted meta-diaphyseal aseptic osteonecroses at both femurs, seizures, as well as posterior reversible encephalopathy syndrome (PRES). All such side effects quickly resolved after therapeutic counteraction of hyperleukocytosis by rapidly installed chemotherapy. Another patient showed abducens paresis, which resolved after break of ATO.

In summary, therapy with ATRA and ATO in our pedia-

tric standard risk patients with APL was generally well tolerated. In-patient treatment duration was mostly only one week. The main complication was the differentiation syndrome, which occurred mainly 6 – 9 days after starting ATO. It was manageable with breaks of ATO, dexamethasone and hydroxyurea and low dose cytarabine. We recommend similar to the Lo Coco trial to give prednisone 0.5 mg/kg/day during induction as prophylaxis for the differentiation syndrome.[1] This new ATRA-ATO treatment should be applied only in experienced clinics accompanied by expert consultation.

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PO038
ACUTE PROMYELOCYTIC LEUKEMIA IN PATIENTS AGED > 70 YEARS: REAL-LIFE RESULTS

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Acute Promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia that, if not quickly recognized, is characterized by a high mortality rate due to a severe bleeding tendency. Therapeutic approaches first based on anthracyclines and then on all-trans retinoic acid (ATRA) and arsenic-trioxide (ATO), have transformed this disease from rapidly fatal to highly curable, even in elderly patients with significant comorbidity. However, only few cases of very elderly APL patients are described in a real-life setting. Therefore, we evaluated the clinical features and follow-up of 22 patients aged > 70 years consecutively diagnosed and treated in our institute from 1991 to 2017. Clinical characteristics at onset were as follows: M/F 12/10, median age 74.9 years (range 70.0 – 85.4), M3/M3v 17/5, median WBC 1.3×10^9/L (range 0.6 – 286), median PLTS 40×10^9/L (range 12 – 302), BCR1/BCR3 8/12. According to Sanz risk score, 9 patients were at low-risk, 8 at intermediate-risk and 5 were high risk; 6/22 patients had concomitant pulmonary diseases 10/22 arterial hypertension, 7/22 a concomitant cardiologic disease, 3/22 diabetes mellitus and 9/22 a previous malignancy. Two patients (9.0%) died very early after admission from gastrointestinal bleeding and fatal cerebral haemorrhage, respectively. The remaining 20 patients received induction therapy consisting of ATRA + Idarubicin in 12 cases (5/12 with reduced Idarubicin dosage), ATRA + ATO in 3 cases and ATRA alone in 5 cases; in this latter group, however, 2/5 needed to add chemotherapy (CHT) based on Mitoxantrone + AraC due to hyperleukocytosis during ATRA treatment. On the whole, 18/20 patients (90%) achieved morphological Complete Remission (CR) after a median time of 45 days (range 28 – 66) and 2/20 (10%) died during induction from septic complications. Among the 18 patients in morphological CR, 16 achieved also a molecular CR after a median time of 118 days (range 51 – 239) while the remaining 2 patients did not perform yet a molecular evaluation. Infective complications were observed in 16/22 patients (5 episodes of FUO, 6 sepsis, 3 cystitis, 4 pneumonitis and 1 oral abscess) while ATRA syndrome occurred in 6/22 patients; in addition, there were 3 episodes of respiratoty failure, 5 episodes of arrythmia (2 paroxystic atrial fibrillations and 1 QT prolongation) and 1 episode of cardiac ischemia. Sixteen patients in CR received consolidation therapy (based on CHT alone in 7 patients, CHT + ATRA in 5 patients, ATO+ATRA in 3 patients and ATRA alone in 1 patient), followed by maintenance treatment in 9 patients: the remaining 2 patients in CR underwent directly maintenance treatment. Four patients had a hematological relapse after 7, 8, 11 and 35 months, respectively, while 2 patients had molecular relapse after 12 and 56 months. At present, 12 patients are still alive, 4 died due to disease progression (3) or senectus while in CR (1) and 2 were lost to follow-up while in CR: 3-year cumulative event-free survival and overall survival were 58.9% (95%CI 36.5 – 81.3) and 63.2% (95%CI 40.8 – 85.6), respectively. In conclusion, ATRA-based treatment of APL is safe and effective also in very elderly patients, with long-lasting disease-free and overall survival

PO039
RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH ARSENIC TRIOXIDE IN A VERY ELDERLY PATIENT WITH SERIOUS COMOBIDITIES

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In January 2008 a 78-year-old men presented in our hospital with fatigue and exertion-related dyspnea. His past history was of venous thrombosis of the left leg, left nephrectomy for tuberculosis and myocardial infarction. Complete blood count showed pancytopenia with white cell count (WBC) of 800/μL, hemoglobin 8.7 g/dL, platelet count of 62.000/μL. The peripheral blood smear revealed severe neutropenia with 5% blasts. Coagulation study and fibrinogen was normal. The bone marrow aspirate showed 95% of blasts whose flow cytometry analysis was positive for CD45, CD13, CD33, CD117, CD9, CyMPO, and negative for CD19, CD14, CD34, CD64, CD11b, CyCD79a, CyCD68, HLA-DR and Lisozima. Real time RT-PCR was positive for PML-RAR and cytogenetics with karyotype demonstrated a t(15;17)(q22;q21) translocation. The diagnosis was of acute promyelocytic leukemia (APL) and given that the WBC count was <10,000/μL, his disease was classified as having low risk. After a careful cardiological evaluation,

he received induction treatment with ATRA plus idarubicin. The clinical course was complicated by pulmonary embolism. In April 2008 molecular bone marrow evaluation was negative for PML-RAR and one cycle of consolidation chemotherapy with ARA-C and idarubicin was administered. After, he received maintenance therapy with ATRA for two years until April 2010 with durable molecular remission for six years.

In June 2016 he presented again for profound fatigue and his complete count blood demonstrated severe neutropenia (WBC 700/mm^3) and thrombocytopenia (PLT 69.000/mm^3). The bone marrow examination and molecular analysis showed relapse of APL. At that time the patients was 82 years old. Considering age and previous exposure to anthracycline, he was treated with combination of ATRA 45 mg/m^2 in 2 divided doses daily and, beginning 10 days later, ATO at reduced dose of 0.1 mg/kg intravenously over 2 hour daily, until hematological complete remission in July 2016. Then, he received arsenic trioxide (ATO) intravenously 5 days per week and ATRA keeping time according to GIMEMA protocol APL0406. Therapy concluded 28 weeks after until February 2017. Throughout the period of treatment, the ATRA was well tolerated and ATO was temporary discontinued when prolongation of the QTc interval occurred and restarted at the same dose at the resolution of toxic effect. Hematological toxicity consisted of a transient neutropenia without fewer infections. A grade 1 diarrhea occurred during every course of therapy, but it did not require a dose reduction of ATO. He achieved molecular complete remission in November 2016. At the last follow up in April 2017 he remained well and molecular CR confirmed.

Here, we report a case of APL in a very elderly patient and with severe previous comorbidities, treated at relapse with ATO + ATRA regimen, achieving a durable remission without serious toxic effects. To date, there are only few reports on treatment of patients of advanced age over 80 years and recently also most studies on ATO single agent or in combination with ATRA did not include so many elderly patients. This case shows that this setting of patients can be sensitive to therapy as well as younger patients and also for them the goal of therapy should be to reach complete remission and cure, if possible. Therapeutic approach with ATO and ATRA was safe, and this demonstrates that even very elderly or frail patients, who are not eligible for common standard therapy, have a chance to reach long-term durable remission or cure.

PO040
EXPERIENCE OF THE ARGENTINIAN GROUP OF TREATMENT OF ACUTE LEUKEMIA (GATLA) IN PEDIATRIC ACUTE PROMIELOCYTIC LEUKEMIA

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Introduction. The APL represents 1% of the pediatric leukemias, and 5-10% of the pediatric AML. The mean age at diagnosis is 7-9 years, with a higher incidence in the Latin population. In Argentina, APL represents near 20% of the pediatric AML. APL is a distinct subtype of AML with different clinical and biological characteristics. The GATLA used the ICC APL-STUDY 01 for the treatment of APL in children.

Objectives. To present the experience of GATLA in the treatment of pediatric APL

Materials and Methods. From March 2007 to September 2016, 78 patients (pts) age < 18 years, were diagnosed with APL; 72 evaluable pts (F: 39 / M: 33) were enrolled for the ICC- APL STUDY 01. Median age: 10.2 y (r: 1 - 17.5 y). The treatment consisted in induction phase with IDA + ATRA until reaching CR, followed by 2 or 3 consolidation blocks according at risk and maintenance phase with Methotrexate + 6-MP with alternated ATRA up to 24 months of treatment. CNS prophylaxis was performed with intrathecal cytarabine according to age. The pts were divided into two risks groups: a) Standard Risk (SR): WBC <10000 / mm^3; b) High Risk (HR): WBC> 10000 / mm^3 or SR patients which, after the 2nd course of consolidation, had positive MRD by RT-PCR. There were 39 SR pts (54.1%) and HR: 33 pts (45.8%). For the SR, median age: 11.9 y (r: 1-17.4 y), mean leukocyte count: 3700/mm^3 (r: 300 - 9300), mean Hb: 8.4 gr / dl (r: 3, 8 -12), mean platelet count: 16,000 / mm^3 (r: 6000-100000). For HR: median age: 9.4y (r: 1.9-17.5 y), mean leukocyte count 27300 / mm^3 (r: 900-273000), mean Hb: 7.4 g / dL (r: 4.8 -13.8), mean platelet count: 23,000 / mm^3 (r: 4000-133000). 4 pts presented variant M3 APL. 28 pts (39%) presented DIC at diagnosis. 13 pts (18%) presented Differentiation Syndrome. 4 pts (5.5%) presented Pseudotumor Cerebrii in Induction. 81% of the pts performed RQ-PCR in the follow up.

Results. 66 pts (92%) achieved complete remission (CR), 92.3% for SR and 87.9% for HR and 1 pts, null response. 5 pts (6.9%) died on induction. Of the 66 pts who reached CR: 9 pts (13.6%) relapsed (4 haematological relapse, 2 molecular relapses, 2 combined BM+ CNS and 1 ALL-T).The global EFS (at 81.8m) was 77.8% (SR: 82.1% and HR: 78.8%) and the overall SV was 85% (SR: 89.7% and HR: 78.8%).

Conclusions: The overall results are acceptable accor-

ding to the international experience. The use of RQ-PCR allows for detecting pts with molecular relapse, in order to be able to achieve an early treatment .

PO041
ARSENIC TRIOXIDE AND ALL-TRANS RETINOIC ACID FOR TREATMENT OF PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA

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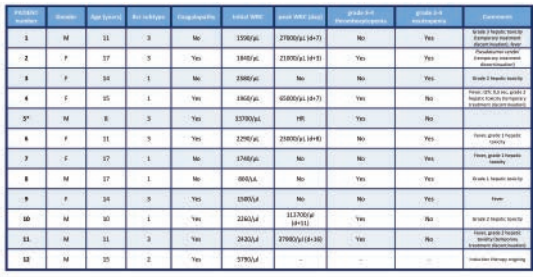
Background. Acute Promyelocytic Leukemia (APL) accounts for approximately 5-10% of cases of childhood Acute Myeloid leukemia (AML), being, however, more frequent in Latin countries. Overall outcomes in terms of complete response (CR), overall survival (OS) and event-free survival (EFS) appear similar in adult and pediatric patients treated with ATRA and chemotherapy regimens. Recently, studies in standard risk (SR) adult APL patients showed that combined therapy with ATO-ATRA leads to impressive cure rates, with a milder toxicity profile if compared with standard chemotherapy regimens. However, experiences in childhood APL employing ATO-ATRA regimens are scarce.

Patients and Methods. Since April 2014, twelve patients have been treated in five Italian Centers with the ATRA-ATO approach reported by the GIMEMA-AMLSG-SAL groups for adult SR APL (Lo Coco *et al*., NEJM 2013). The only difference was a lower ATRA dose (25 mg/m2/day). Median age at diagnosis was 14 years (range 8-17) with 11 out of 12 children allocated to the SR group (WBC < 10,000/ l) and 1 to the high-risk (HR) group (WBC > 10,000/ l). During induction therapy hydroxyurea (20-60 mg/kg/day according to the WBC count) was used to control hyperleukocytosis (WBC > 10,000/ l), while prednisone 0.5 mg/kg/day (from day +1 to day +15 of induction) was given in order to prevent differentiation syndrome. Two patients (patients n.6-7) are currently undergoing consolidation therapy, while patient n.12 is completing induction therapy.

Results. Coagulopathy was present at diagnosis in 7/11 patients and it resolved during induction without any major complication. Hyperleukocytosis during therapy occurred in 6 out of 11 SR patients with a peak on day+8. No case of differentiation syndrome was recorded. Hepatic toxicity consisting of temporary increase of ALT/AST levels, occurred in 7 patients (grade 1, 2, 3 in 3, 3 and 1 patients respectively), while only 1 patient experienced transient QTc interval prolongation (0,5 sec). Pseudotumor cerebri was observed in 1 patient during consolidation phase. Hematologic toxicity of different severity was observed in all patients (see also Table 1). Temporary treatment discontinuation was needed in 4 patients due to grade 3 hepatic toxicity (patient n.1), prolonged QTc interval (patient n.4), fever (patient n.11) and pseudotumor cerebri as mentioned. Median hospital-stay was 33 days (15-36 days) during the induction phase. All the 11 evaluable patients achieved hematologic complete remission (CR) after induction therapy. All the 9 patients who completed treatment achieved complete molecular response (CMR). With a median follow-up of 16 months (range 4-41) neither hematological, nor molecular relapses occurred.

Conclusions. This collection of pediatric cases is, to the best of our knowledge, the largest analyzed so far using the chemo-free ATRA-ATO regimen. Our results indicate that the ATRA-ATO combination is safe and effective also in childhood APL. Acute treatment-related side effects were hematologic and hepatic toxicities which were transient and manageable. Although only one HR child was treated with this approach, the favourable outcome suggests that this subset of patients may also benefit from this chemo-free treatment.

Table 1.



*myc duplication.
HR: high-risk; M:male; F:female

PO042
OUTCOMES IN ELDERLY APL PATIENTS: A PERSONALIZED TREATMENT APPROACH ALONG WITH EXPERT SUPPORT MIGHT REDUCE EARLY DEATHS

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Background. The excellent outcomes in APL are not

seen in elderly patients where early deaths (ED)in trials are 10-18%. Population based registry data shows that ED rate in elderly patients is even higher at 24-50%. The one year survival was <40% in patients >60 years in Swedish population data. We report the outcome of patients >60 years from our experience.

Methods. Retrospective chart review was performed with IRB approval of 138 patients treated at leukemia treatment hospitals in GA, SC and neighboring states. Newly diagnosed patients were treated using a simplified set of treatment guidelines along with expert support designed to decrease ED. There were no exclusion criteria in this prospective trial. Given the comorbidities in this "real world"elderly population, dose reductions were necessary. We documented the doses of ATRA, ATO, and idarubicin given to patients ≥60 at diagnosis, and then calculated the percentage dose reduction the patient received, if any. For our calculations, standard doses were 45 mg/m^2/day for ATRA, 0.15 mg/kg/dose for ATO, and 12 mg/m^2/dose for idarubicin. The target dose reduction for patients' ≥60 in the second half of the study was 25 mg/m^2/day for ATRA and 0.075 mg/kg/dose for ATO. In morbidly obese patients, the BSA was capped at 2.0 and dosing weight for ATO at 100 kg.

Results. Between 7/2013 and 4/2017, 138 patients were treated at 4 large leukemia centers and 30 community hospitals. Fifty-three patients (38.4%) were >60, with a median age of 69. Male to female ratio was 1:1. Median WBC was 2.3/mm^3 (0.3-38); 93% were low risk.25 (47%) were treated in our institution and28 (53%) weremanagedin 18 other centers. Of this group, n=27 were ages 60-69, n=19 were 70-79, and n=7 were >80. 30 (56.6%) patients had scores of > 5 on the age adjusted Charlson Comorbid Index (range 2-12). Dose modifications were necessary given the high comorbidities which are not usually the norm in clinical trials due to exclusion criteria. A total of 53 patients (100%) received ATRA, 43 (81%) received ATO, and 7 (13%) received idarubicin (Ida). For ATRA, n=5 (9%) received an initial dose reduction of 10-24%, n=13 (24.5%) received reduction of 25-49% and n=7 (13%) received a reduction of ≥50%. For ATO, n=2 (4.7%) received a reduction of 10-24%, n=10 (27.9%) received a reduction of 25-49% and n=14 (32.6%) received a dose reduction of ≥50%. The remaining patients received full doses. For six patients, the dose of ATRA (n=1), arsenic (n=5), and (Ida) (n=1) was not provided. Excluding two patients, one a Jehovah's Witness who refused transfusions and the otherwe were consulted 12 days after diagnosis with multi-organ failure, there were nine deaths during induction (17.6%). There were 6 late deaths from second cancer (n=1), relapse (n=1) and non APL related deaths (n=4).There were 3 relapses (2 high risk), none of whom received dose reductions and 1 refused consolidation. With a median follow up of 562 days the 1 year survival was 74.5% and overall survival was 70.6%.

Conclusions. One year relative survival in elderly APL patients is dismal with population based Swedish and SEER data showing rates <50%. Age and comorbid conditions dictate that amore personalized approach with dose reduction could result in better tolerance and improve outcomes in the elderly. A simplified treatment algorithm along with expert support has the potential to decrease induction mortality (17.6%) and improve population wide survival (1 year 74.5%).

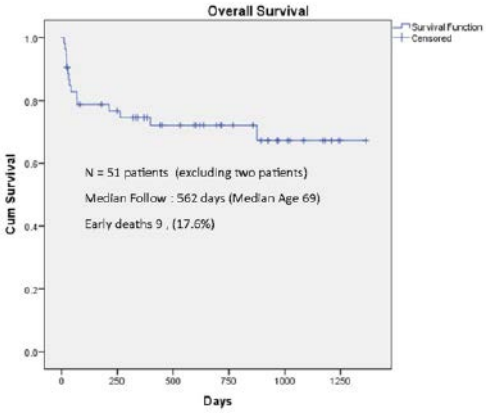

Figure 1.

P0043
VERY ELDERLY ACUTE PROMYELOCITIC LEUKEMIA: A MULTICENTRIC EXPERIENCE

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Background. Acute promyelocytic leukemia is a unique acute leukemia in terms of outcome. However elderly population has limited therapeutic options due to biology of disease, performance status and presence of comorbi-

dities. Recently it is been published fairly good tolerance and efficacy with ATO+ATRA combination in elderly population, however there is still scarce information on verly elderly (≥75y) that it might be underestimated in most registries as most phisicians belive that is not worth to treat this AML subset population.

Objective. To analyze phisicians attitude in terms of treating this very elderly APL population in Spain and to analyze results in terms of efficacy and toxicity of treated patients with PETHEMA chemotherapy based protocols between 1997 and 2016 compared with the untreated patients

Methods. Selection of patients over 75 years old with APL reported to the Spanish National Registry in PETHEMA group over the last 19 years. Analyze epidemiologic characteristics and disease features in the very elderly APL population and describe percentage of patients treated according to investigators criteria. Analyse response rate in treated patients, percentage of induction deaths and OS and DFS in responders. Satistical analysis is been performed with SPSS v23.

Results. Between 1997 and 2016, 95 patients have been selected as truly APL according to WHO crietria. Median age was 79 (75-90) years old; 47, woman and 48,men. 21 cases were secondary APL. 23 patients recieved no treatment or only BSC strategies according to phisicians decission and 21 recieved ATRA alone in addition to BSC. 48 patients recieved chemotherapy regimens according to PETHEMA-96/99/05/12 protocols-; slightly younger age in chemotherapy group (78 *vs* 81) with no other significant differences between both groups according to APL clinical features at diagnosis nor biological features. Of those who recieved chemotherapy regimen (48), 82% achieved CR after induction therapy; on the other hand there is a 31% of induction deaths. Worth to mention that only 30% accomplished with all consolidation and maintenance therapy according to protocols mentioned due to toxicity. Relapse rate in chemotherpy treated patients is 7%. Impact of chemotherapy treatment in this population demostrated significant benefit in terms of OS in those achieving CR with median survival of 39 months (0-115) vs 3,5 months (0-30) in untreated (BSC, 12 days (0-82); ATRA "only", 185 days (3-922)). Patients who recieved "only ATRA" treatment, had 47% CR, all with Positive PCR after 2 months therapy, however 70% relapsed. With a median time to relapse of 5 months (0-22).

Conclusions. Treating very elderly patients with APL is worth to be considered. Nowadays, other treatment options avoiding antracicline based chemotherapy, weather in clinial trial or with ATO+ATRA regimen should be indicated upfront whenever possible.

PO044
APL IN THE ELDERLY: EFFICIENT CONSOLIDATION THERAPY USING THE SHORT "MATTHEWS" COURSES OF ARSENIC AND ATRA

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During the past 7 years, we have treated 9 senior patients aged 71-87 years (median 75 yrs), 3 males and 6 females. All of them carried the PML-RARa fusion (6 with bcr1 and 3 with bcr3 PML breaks), 2 had the variant microgranular morphology. The median WBC count was 1.0 (0.2-30.4) G/l; two patients had leukocytosis > 10 G/l, both of whom had M3v morphology and the FLT3 internal tandem duplication. Two patients died during induction (including one of the high-risk patients).

The induction treatment consisted of standard dose ATRA in all instances. In 2 patients, ATRA was given as monotherapy. In 6 patients, a reduced dose of idarubicin (25-75% of the AIDA protocol dosage) was added. In 1 patient (who died within 5 days of treatment due to myocardial infarction), arsenic trioxide (ATO) was administered during induction in addition to ATRA. All 7 patients who did not succumb during induction achieved complete remission. All patients were then consolidated with six 10-day protocols of ATO 10 mg daily i.v. + ATRA (in courses 2-6) as described by V. Matthews *et al*. (Blood, 2006) – thus, the patients were 10 days on and 20 days off ATO therapy during consolidation. All patients achieved a sustained molecular remission (PML-RARa negativity in bone marrow samples and normalization of WT1 expression in peripheral blood), latest following the second ATO (+ ATRA) course. Only mild degrees of leukopenia and anemia were observed, without any cardiac problems (with regular ECG, K+ and Mg++ monitoring). After finishing the six "Matthews" protocols, all patients then received 4 to 6 courses of ATRA (15 days every 3 months). All post-remission courses were given on out-patient basis, without a single hospitalization day; the adherence to the protocol was 100%. The patients had a perfect quality of life. All 7 patients remained in molecular remission 4-86 (median: 60) months after diagnosis.

Our study shows that it is appropriate to aim at precise diagnosis including PML-RARa detection even in senior patients with AML, as APL is curable in most cases and its diagnosis should not be missed. Seeing to the contraindications of chemotherapy, ATO + ATRA seems to be the optimal consolidation option in senior patients. The short courses of ATO administered on 10 consecutive days according to Matthews are advantageous especially in the elderly, as they are fully feasible and devoid of serious toxicity (compared to longer ATO courses). Yet, the quality of remissions is still excellent, with no molecular relapses being observed within the median of 5 years of follow-up.

PO045
TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA IN PATIENTS AGED OVER 60 YEARS-EXPERIENCE FROM A HUNGARIAN CENTER

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Introduction. Clinical presentation of acute promyelocytic leukemia (APL) shows certain differences compared to non-APL leukemia. Although median age of patients at disease discovery is generally younger, we still have to manage several elderly patients. Treatment approaches for patients with other forms of acute myeloid leukemia are very limited at advanced age, but targeted molecular therapy provides us with a curative treatment in older individuals.

Patients and Results. We treated 16 patients with APL between 2008 and 2016 in our hematological center in Hungary, among them 5 patients aged over 60 years. Median age at diagnosis was 53 years. 80% of our patients over 60 was low-intermediate risk compared to 45% observed in our younger patients. Cumulative Illness Rating Scale (CIRS) Score of our geriatric patients ranged between 0-18. We apply generally PETHEMA/HOVON LPA2005 protocol to treat our patients, with the corresponding risk adapted consolidation regimen. In one patient out of the 5 we were able to complete the full therapeutic regimen, in two patients we had to reduce the cycles of consolidation and maintenance due to neutropenic infections and septicemia. Our oldest patient (aged 83 at diagnosis) with a CIRS Score of 18, acquired active pulmonary tuberculosis during induction, thus he received a low-dose consolidation protocol in an outpatient setting, with no maintenance. One patient died at the beginning of induction therapy due to sudden cardiac arrest. All the surviving patients achieved complete remission, with no relapse observed.

Conclusions. Targeted chemotherapy to treat APL can be successfully administered to older patients, with a high remission rate. Our experience shows that - similar to observations in international studies - the main problem in the treatment of APL in elderly remains high treatment related morbidity, while disease relapse is rather rare. Despite of problems related to concomitant diseases and side effects of chemotherapy, with the appropriate determination of therapy intensity we can achieve durable remission in our old APL patients.

PO046
ASSESSMENT OF ARSENITE-RESISTANCE MUTANT PML PROTEIN SOLUBILITY CHANGES BY PHENYLARSINE OXIDE

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Arsenic trioxide (As_2O_3) has been accepted as a standard treatment for the patients with acute promyelocytic leukemia (APL) in world, and its molecular mechanism has also been largely investigated. However, it has been reported that As_2O_3 resistance patients are frequently found in relapsed APL after consolidation therapy, which is due to the point mutations in B-box type2 motif of PML gene. In the present study, we for the first time establish whether organic arsenic species phenylarsine oxide (PAO) could induce the mutant PML-IV (A216V) protein solubility changes and degradation. Here, three different PML protein variants (*i.e*., PML-IV, PML-V and muatant PML-A216V) were overexpressed in HEK293T cells and then exposed to PAO in time- and dose-dependent manners. Interestingly, PAO is found to have potential effect on induction of muatant PML-IV(A216V) protein solubility changes and degradation, but no appreciable such effects have found following exposure to high concnetrations of iAsIII, dimethylarsinous acid (DMAIII) as well as adriamycin (doxorubicin) even though they causes cell death. Our current data strongly indicates that PAO have good effects on the mutant PML protein solubility changes, it may be helpful to improve the therapeutic strategies for arsenic-resistance APL treatments in near future.

PO047
RELAPSED APL AND ITS TREATMENT OUTCOME – A STUDY FROM EASTERN INDIA

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With the current standard of care, relapse rate is considered to be quite low in Acute Promyelocytic Leukemia (APL). However, literature suggests that 10-15% cases relapse, with most of the patients having high risk disease at diagnosis. In our institution, 87 patients were diagnosed with APL from 1.4.2012 to 1.4.2017. Most of the patients received anthracycline based therapy as their first line therapy. Recently we have shifted to Arsenic + ATRA based therapy for patients with low and intermediate risk (data presented elsewhere). The relapsed APL cases in our institution receive ATRA + ATO based therapy.

A Total of 45/87 patients had successfully completed their treatment in our institute over the mentioned period. Treatment abandonment was quite high because of financial and logistic issues. Of these 45 patients, 7 (15.5 %)

had relapsed. Summary data of the relapsed patients are given in the Table 1.

Table 1.

	Low/ Intermediate risk	High risk	Total
Relapsed Rate	2/26 (7.7%)	5/19 (26.3%)	7/45 (15.5%)
Median Age (Years)	25.5	26	25.7
Sex (M:F)	0 : 2	4 : 1	4 : 3
Median time of Relapse (Month)	8 Month	6.4 Month	7.2 Month
Molecular/Haematological relapse	2 : 0	4 : 1	6 : 1
CNS relapse	0	1	1 (2.2%)
Remission status	2/2 (100%)	3/5 (60%)	5/7 (71.4%)
Mortality during Induction	-	2 (28.5%)	2 (28.5%)

In the low/intermediate risk category, 100% patients were able to achieve a second remission (CR2) with no induction related mortality. However in the high risk category, one patient was lost to follow up and presented with haematological relapse. The condition of the patient was critical at presentation and he expired before initiation of definitive therapy. The second patient in high risk group was lost due to sepsis during induction therapy.

PO048
ACUTE PROMYELOCYTIC LEUKEMIA RELAPSING AS MYELOID SARCOMA WITH FLUCTUATING MINIMAL RESIDUAL DISEASE LEVELS AND LYMPH NODE INVOLVEMENT: A CASE REPORT

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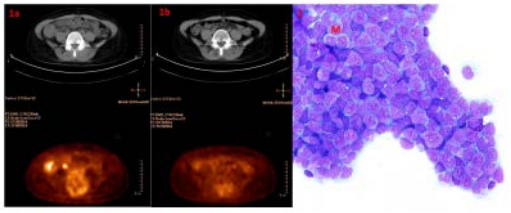
A 43 year old female patient was diagnosed with bcr3 transcript-positive, intermediate risk, aPML in April 2014 and was treated according to AIDA2000 protocol. After the end of cycle 4, patient remained MRD negative until September 2015, when a PB MRD evaluation came out positive. Subsequent PB MRD evaluations performed between October 2015 and March 2016 were persistently positive with fluctuating values, bone marrow MRD being unexpectedly lower than PB MRD. No other features suggestive of relapse were noted; such unusual MRD behaviour without quick progression to overt relapse is rather atypical for aPML, thus we questioned whether these findings could be attributable to technical issues in MRD measurements and had a different referenced laboratory perform duplicate MRD testing. MRD positivity was confirmed with bcr3/ABL1 ratios comparable to our results. In April 2016, after the onset of worsening lumbar pain, an MRI scan revealed a solid mass infiltrating L3, L4 and L5 with medullary compression and soft tissues infiltration. 18FDG-PET scan showed the presence of two distinct lesions with high 18FDG uptake affecting D5, L3, L4 and L5. Additionally, more high 18FDG uptake foci attributable to lymph nodes were detected in the internal and external iliac region (Figure 1a). Fine needle biopsy of the paraspinal lesions confirmed extramedullary aPML relapse. A BM aspirate showed persisting morphologic CR, although with rapidly increasing MRD levels. Patient received reinduction with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA); molecular MRD negativity was achieved at the end of induction. Subsequently, 20 Gy radiotherapy was applied on lumbar and dorsal lesions and patient went on to receive ATO-ATRA consolidation (4 cycles). FDG-PET scan repeated in September 2016 showed improvement (Figure 1b). However, end of treatment BM MRD testing came out positive.Few weeks later, following the onset of right upper limb and perioral paresthesia and vomiting, an MRI scan showed extensive leptomeningeal enhancement. Accordingly, CSF examination showed massive promyelocytic infiltration (Figure 2).

High dose cytarabine salvage was administered (along with CNS-directed intrathecal treatment) as a bridge to allogeneic stem cells transplantation; unfortunately, patient died during aplasia due to Stenotrophomonas maltophilia pneumonia. Here we report an unusual case of aPML relapsing as myeloid sarcoma without overt bone marrow involvement. Lymph node involvement – although not histologically confirmed – is somewhat intriguing from the biological point of view being an extremely rare finding in aPML, possibly hinting a distinct and perhaps more aggressive disease profile. Fluctuating levels of MRD over a several months period in our patient represent a very unusual finding given that most aPML molecular relapses tend to progress to overt haematological relapse within weeks. The fact that PB MRD was persistently higher than BM MRD is intriguing; vascularization of the mass might have caused transcript spillage into PB resulting in higher PB MRD levels. Myeloid sarcoma is a rare yet possible occurrence in aPML at relapse even in the absence of overt BM involvement. Our experience warrants the need of careful evaluation for patients with seemingly fluctuating MRD levels. Moreover, such occurrences could be interpreted as manifestations of a uniquely aggressive clinical behavior, requiring careful considerations regarding therapeutic decisions.



1. FDG-PET/CT scan demonstrating the paraspinal lumbar lesion along with iliac lymph nodes positivity before (a) and after (a) ATO-ATRA reinduction followed by radiotherapy; 2. CSF cytospin showing massive infiltration by promyelocytes (modified May-Grunwald Giemsa stain) with detectable mitotic figures (M)

Figure 1.

PO049
THERAPY-RELATED ACUTE PROMYELOCYTIC LEUKEMIA. EXPERIENCE IN A SINGLE INSTITUTION IN ARGENTINA

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Introduction. Therapy-related AML (t-AML) accounts for 10-20% of all cases of AML, most of them with MLL-abnormalities, with high rate of morbidity-mortality. Therapy-related acute promyelocytic leukemia (t-APL) has been reported over the last decades, after exposure to cytotoxic and/or immunosuppressive agents administered for treating prior malignancies or autoimmune diseases. However, APL is not the most frequent subtype of t-AML.

Objective. Our aim was to analyze clinical/biological characteristics and outcome of two patients with t-APL following treatment for relapsed ALL.

Methods. From January-1990 to June-2017, 95 patients with APL were diagnosed in our Institution. Two of them (2%) were t-APL. We analysed clinical/biological features and outcome of these 2 t-APL cases.

Results. Case 1: A 2 year-old boy with diagnosis of Common ALL (46,XY) who presented a testicular relapse showing the same phenotype of the first diagnosis. Case 2: A 5 year-old girl who was diagnosed with a Common ALL (TEL-AML1 +). She presented a bone marrow relapse. Both patients had been treated with a BFM-based ALL protocol and after a second treatment which included a weekly-rotational continuation phase with etoposide and teniposide every other week, they achieved second CR. They also received preventive CNS-radiotheraphy and Case 1 also therapeutic testicular- radiotherapy. Cumulative doses of anthracycline was 280 mg/m2. After a latency of 66 and 110 months from first diagnosis, both patients presented pancytopenia, with a massive bone marrow infiltration by promyeloblasts and the presence of PML-RARA transcript was detected. Treatment was adapted with ATRA and liposomal doxorubicin in case 1 and with ATRA plus ATO in the second one. Both patients achieved CR, case 1 remains in molecular CR at +104 months and case 2 at +1 month from t-APL diagnosis. They present a good performance status.

Conclusions. 1- t-APL should be considered among different t-AML subtypes. 2- Treatment of t-APL should be adapted considering previous cumulative doses, mainly anthracyclines. 3- t-APL probably has better survival probabilities than other t-AML. However, more data is needed for a better definition of the prognosis of this particular subset of patients.

PO050
LONG-TERM FOLLOW-UP OF FIRST LINE ARSENIC TRIOXIDE IN COMBINATION WITH ALL-TRANS RETINOIC ACID COMPARED TO CHEMOTHERAPY IN COMBINATION WITH ALL-TRANS RETINOIC ACID IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA: MONOCENTRIC EXPERIENCE

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Introduction. Acute promyelocytic leukemia (APL) is a variant of AML characterized by t(15;17). The discovery of the molecular pathogenesis has led to the first targeted therapy for acute leukemia: all-trans retinoic acid (ATRA). It is usually associated to anthracycline-based chemotherapy obtaining high response rates, but some potential long-term sequelae are described. The introduction of acid trioxide (ATO) tries to obviate such complications. We present our experience of APL patients (pts) treated with ATO plus ATRA compared to pts treated with chemotherapy plus ATRA.

Description. From January 2009 we treated 12 APL pts with ATO plus ATRA regimen according to GIMEMA protocol APL0406 (Platzbecker U, J Clin Oncol. 2016). Their characteristics are summarized in Table 1 together to those of the control cohort treated with chemotherapy plus ATRA according to AIDA-2000 (Lo Coco F, Blood 2010). The treatment of ATO plus ATRA was well tolerated: brief interruptions of ATO were registered in 7 pts, ATRA syndrome was described in 5 pts. This syndrome was also registered in the control arm in 6 pts. During the induction phase, we also registered in the first arm 2 thrombotic events, 2 HSV infections and 1 ATRA myopathy; in the control arm all but 4 pts experienced fever requiring of antibiotics, 5 hemorrhagic complications, 1 thrombophlebitis and 1 benign endocranial hypertension.

All pts obtained molecular remission after a median time of 3 months in both groups. In the first arm, during consolidation only 2 pts experienced a reduction of ATO dosage due to QTc prolongation and other adverse events were benign endocranial hypertension (1 pt), mild hepatotoxicity (1 pt) and herpes infection (1 pt). In the control arm during consolidation 9 pts showed neutropenic fever, 2 thrombotic events, 1 mild hepatotoxicity; during the maintenance phase hepatotoxicity of different grades and neutropenia were common.

All pts of the first arm remained in molecular response at a median time of 16 months (range 2-91) except 1 pt who showed the reappearance of PML-RAR in the bone marrow after 11 months; he restarted ATO plus ATRA and he achieved molecular CR at the 3-month control. When considering the control arm all pts were in molecular response for a median time of 43.5 months (range 30-97) but 2 developed MDS after few months and 3 years from the end of the maintenance phase, respectively. All pts of the first arm are alive and in response at a median follow-up of 19 months (range 4-94) and no late effects were registered. In the control arm 2 pts who developed MDS

died, the others are alive after a median time of 47 months (range 35-100).

Discussion. ATO plus ATRA regimen shows advantages in comparison to chemotherapy; it allowed to treat pts in which chemotherapy could not be the first choice or it could even not be applicable including secondary APL. This approach allowed to reduce hospitalization and risk of neutropenic fever. A major impact of transfusion support was observed: only 9 pts in the first arm required platelets or red blood cells versus all pts in the control arm, also requiring fresh frozen plasma; no one of the first arm required transfusion during consolidation versus 9 pts in the control arm.

Conclusions. The association of ATO to ATRA is the first experiment of chemo-free regimen to treat acute leukemia and APL has been modified from a highly fatal disease to a highly curable one even without chemotherapy also reducing the risk of MDS.

Table 1.

		First arm (ATO plus ATRA) 12 pts	Second arm (Chemotherapy plus ATRA) 12 pts
Median age (years)		45.5 (range 24-62)	42 (17-60)
Gender M/F		9/3	7/5
WBC count (mmc)		1070 (range 650-9770),	3350 (range 800-117000)
Hemoglobin (g/dl)		9.1 (range 6.1-12.8)	9.9 (range 5.3-14.5)
Platelets count (mmc)		25.5 (range 9-136)	23 (range 7-119).
Risk category	High Intermediate Low	0 9 3	4 6 2
ISTH-DIC score high (>5: DIC probable)		6 pts	8 pts
Molecular analysis	bcr1 bcr3	8 4	5 7

PO051
THERAPY-RELATED AML WITH DIC(5;17) FOLLOWING TREATMENT FOR APL WITH T(15;17): TWO INDEPENDENT MYELOID MALIGNANCIES INVOLVING CHROMOSOME 17 TRANSLOCATIONS

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We present a case of a 58-year-old man who developed t-AML with a dic(5;17) translocation following treatment for APL. He initially developed pancytopenia and was diagnosed with low-risk APL with a t(15:17) translocation. He received induction with all-trans retinoic acid and arsenic trioxide. After 9 days, he developed elevated pancreatic enzymes and QTc elongation. Arsenic trioxide was discontinued and he completed induction with 4 cycles of idarubicin. Following induction, his bone marrow contained no blasts and no immunophenotypic evidence of leukemia. FISH was negative for t(15:17). He received consolidation with one cycle each of idarubicin and mitoxantrone.

He remained asymptomatic with no evidence of PML-RAR fusions on PCR or FISH for over three years. He then developed pancytopenia with pronounced thrombocytopenia and peripheral blasts. A bone marrow biopsy showed t-AML with 20% blasts. The karyotype contained a dicentric (5;17)(q11.2;p11.2) translocation resulting in 5q deletion and 17p deletion, along with loss of one copy of chromosome 11, add(19p), and a marker chromosome. Three of 20 karyotyped cells showed tetraploidy. Cytogenetics showed deletion of 5q31 in 91% of cells, MLL amplification in 95% of cells, and loss of TP53 in 90% of cells. There was no evidence of PML-RAR fusion by FISH or PCR. FLT3 ITD and TKD mutation testing was negative. Next-generation sequencing showed FLT1-ETS1 fusion, a TP53 mutation, and an equivocal EMSY mutation.

He was given induction therapy with cytarabine and daunorubicin after determining that this would not exceed a lifetime anthracycline dose of over 450mg/m2. A repeat bone marrow biopsy showed that he continued to have persistent t-AML with 1.3% residual blasts. He had no evidence of disease in the CSF. He then received an investigational agent on an investigational protocol prior to stem cell transplantation. He underwent conditioning with fludarabine and melphalan and received plasma-depleted peripheral blood allogeneic hematopoietic stem cells from an unmodified unrelated donor. He had a complicated post-transplant course but engrafted to 100% donor, however, blasts were detected by flow cytometry. He went on to develop renal failure and continued to deteriorate. He was placed on hospice, where he passed away roughly 6 months after his relapse.

This patient presents a rare case of t-AML following treatment for APL that resembles a case reported by Hatzis et al in 1995. In that case, a 57-year-old woman with APL received an anthracycline-heavy induction and consolidation regimen. She achieved a complete remission, but developed therapy-related RAEB MDS with a dic(5;17)(q11;p11) roughly 2 years later. She rapidly progressed to aggressive AML and passed away 6 months later.

There is striking similarity between these two cases. Each patient developed AML 2-3 years after completing treatment for APL with anthracycline-based regimens, and, in both cases, the AML harbored a dic(5;17)(q11;p11) translocation. The similarity is particularly illuminating given that our patient had the benefit of more modern treatment regimens for both his APL (though he did ultimately require anthracyclines), and for his AML. This case, in addition to the other cases reported in the literature, suggest that therapy-related AML with dic(5;17) should be recognized as a karyotype with a poor prognosis. The biological implications of the dic(5;17) translocation in t-AML will be discussed.

PO052
SECONDARY MALIGNANCY AFTER TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA: A REPORT BY THE RETE EMATOLOGICA PUGLIESE

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Introduction. APL patients presented a high percentage of curability. Long- term survival could lead to the possibility of emergence of late complications such as secondary malignancies (SM). In 2002 Latagliata et al reported 5 cases of therapy-related myelodysplastic syndrome/ AML in a cohort of 77 patients in CR after chemotherapy according to GIMEMA 0389 and AIDA trials. In the same year Pagano et al reported 4 cases of non hematological - SM (kidney, bowel, melanoma and thyroid, respectively) in a cohort of 1145 patients recruited in the GIMEMA APL trials between 1982 and 1997. The estimated cumulative incidence of a SM at 5 and 10 years was lower than expected (0.43, 95% CI 0.16-1.15).

Description. We retrospectively studied 240 APL patients treated between 1996 and 2016 within 7 Hematologic Centers in the Apulia region (Italy). Patients had received:

1) Chemotherapy + ATRA: 190 patients
2) ATO-ATRA: 35 patients
3) Chemotherapy – ATO-ATRA: 10 patients
4) ATRA only: 5 patients

Six out of 240 patients (2.5 %) , 3 males and 3 females, median age 55 (range 47- 71) years developed a SM (kidney cancer , pancreatic cancer, B- chronic lymphocytic leukemia (B- CLL) , ovarian cancer , AML , breast + colon cancer in one patient, respectively). All these patients were treated according to the GIMEMA protocols AIDA 2000, APL0493, APL 0389 (Chemotherapy + ATRA). The median latency between APL diagnosis and SM was 26 months (range 19 - 228 months). The median follow-up was 40 months (range 12- 240 months) . Four out of six patients died from progression of SM (without sign of APL relapse) after 6,8 , 12 and 40 months respectively. Two patients are still alive without signs of relapse of APL after 8 (ovarian cancer) and 228 (B-CLL) months, respectively.

Conclusion: In our experience the number of SM in APL patients is low (2.5%) suggesting , as in previous reports, that APL treatment (chemotherapy + ATRA) is not relevant in inducing the onset of a SM. No neoplasms were observed in the ATO-ATRA group, but further follow up from recently conducted randomized trials are required to confirm our observation in this relatively new regimen.

PO053
THERAPY-RELATED MYELODYSPLASTIC SYNDROME AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENT WITH ACUTE PROMYELOCYTIC LEUKEMIA IN SECOND REMISSION – A CASE REPORT

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In June 2012, acute promyelocytic leukemia (APL) with t(15;17) was diagnosed in 55 years old male. There were no clinical or laboratory signs of coagulopathy. Based on white blood cell WBC=0.79×10^9/L) and platelet counts (Plt=13x109/L), the disease was classified as intermediate risk. He underwent induction and three consolidation cycles according to the risk-adapted protocol (HOVON 79 APL/PETHEMA LPA 2005) with idarubicin (mitoxantrone [MZT] in the second consolidation) and all-trans-retinoic acid (ATRA) from June to October 2012. Persistent complete molecular remission (CRm) was achieved after induction and remained throughout regular check-ups. Maintenance therapy (MNT) with daily 6-mercaptopurine (6MP) and weekly methotrexate (MTX) started in November 2012, while fifteen-days cycles of ATRA in MNT started in January 2013 and continued every three months. During first six months of MNT, MTX was interrupted for two times (first time due to the elevation of hepatic transferases, the second time in a periprocedural period of elective cholecystectomy because of symptomatic cholecystolithiasis). The re-challenge with MTX in July 2013 resulted again in hepatic transaminases elevation, so it was permanently discontinued. ATRA and 6MP were continued but with poor compliance. In December 2013 relapse of APL was confirmed. Reinduction therapy with high-dose cytarabine, MZT and ATRA resulted with second CRm. After consolidation with mitoxantrone, intermediate dose cytarabine and 15 days of ATRA, adequate hematopoietic stem cell graph was collected. In May 2014, he underwent autologous hematopoietic stem cell transplantation with myeloablative conditioning regimen (busulfan and cyclophosphamide) while still being in second CRm. In posttransplant period persistently elevated gamma glutamyl transferase (GGT) was noticed at levels around 200. In check-up, GGT levels remained at same levels, laboratory signs of iron overload were found. Hemochromatosis was excluded. In October 2015 ultrasound showed signs of fatty liver, splenomegaly and dilatated the main branch of portal vein. Bicytopenia (WBC 2.5 and Plt 95×10^9/L) was observed. CRm of APL was persistent, with normal bone marrow cytomorphology and karyogram. In September 2016 bone marrow examination (that was normal in previous check-ups until that point) reveals 3% blasts and megablastoid erythropoiesis in >50% erythroid lineage. Bone marrow karyogram showed isolated monosomy 7 in five of 30 metaphases confirmed by FISH. APL was still in CRm. The final diagnosis was therapy-related myelodysplastic syndrome (t-MDS) with revised international prognostic score (IPSS-R) of 4.5. Upfront hemato-

poietic stem cell transplantation (HSCT) was selected as the optimal modality of treatment. Potential sibling or adequate unrelated donors were not available. Therefore, haploidentical HSCT, with son as a donor, was indicated. In March 2017 Coombs positive hemolytic anemia and chronic hepatitis with a starting fibrotic changes. Viral etiology was excluded and pathomorphology of liver tissue could be explained by toxic drug influence. Due to leukocytosis (35×10^9/L), after exclusion of AML transformation, 5-hytroxyurea was introduced. At the time of submitting the abstract, the patient is admitted for HSCT.