
SECOND ANNOUNCEMENT
" Progress and Constraints in treating APL in India”
7th INTERNATIONAL SYMPOSIUM ON
ACUTE PROMYELOCYTIC LEUKEMIA
ROME, September 24-27, 2017
Chairmen: F. Lo-Coco, M.A. Sanz
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TATA MEDICAL CENTER
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Disclosures of Dr Mammen Chandy

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
nil	nil	no	nil	no	no	no	nil

Outline of the Presentation

- Data from Tata Medical Center Kolkata.
- What has changed in India
- MDRO
- Diagnosis of APL
- Choosing protocols for APL in India
- Preventing and managing the differentiation syndrome
- Starting an APL registry for India


AFGHANISTAN
Intl. Boundary
State Boundary
States
Country Capital
State Capital
Major Centres
NEW DELHI
SHIMLA
Cuttack
CHINA
PAKISTAN
TIBET
NEPAL
BHUTAN
BANGLADESH
MYANMAR
SRI LANKA
ARABIAN SEA
BAY OF BENGAL
INDIAN OCEAN
Gilgit
JAMMU & KASHMIR
SRINAGAR
Leh
Gulmarg
Jammu
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Khajuraho
Gaya
Bhuj
GANDHINAGAR
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Ahmadabad
MADHYA PRADESH
BHOPAL
Ujjain
Jabalpur
GUJARAT
Rajkot
Indore
Vadodara
Junagadh
Betul
Bilaspur
CHATTISGARH
Raurkela
Surat
Nagpur
Bhilai
RAIPUR
Sambalpur
DIU
DAMAN
SILVASSA
(DADRA & NAGAR HAVELI)
Nasik
Aurangabad
MAHARASHTRA
Nanded
Ulhasnagar
MUMBAI
(Bombay)
Pune
Solapur
Bider
HYDERABAD
Kolhapur
Gulbarga
Vijayawada
Guntur
Belgaum
Dharwad
Hubli
PANAJI
GOA
Marmagao
ANDHRA PRADESH
Cudapah
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KARNATAKA
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Machilipatnam
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Cuttack
Paradwip
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Gangtok
Darjeeling
Siliguri
Nalbari
Darbhanga
Kishanganj
Guwah
Patna
BIHAR
MEGHALAYA
Gaya
Bangladesh
JHARKHAND
TRIPUR
Ranchi
WEST BENGAL
Kolkata
Chittag


TATA MEDICA CENTER


MEDICAL CENTER

Children's Ward

STEM CELL CRYO -PRESERVATION LABORATORY

APL 2011 to 2017

Tata Medical Center
Kolkata

Patients diagnosed at TMC

Patients	Number	Percentage
Total	80	
Pediatrics Unit	16	20%
Only for diagnosis	11	13.75%
Treated by the adult team	53	66.25%

Hematological parameters at presentation

Parameters	Median	Range
Hemoglobin : median [range]	8.75	(3.7 – 12.5)
WBC count : median [range]	19500	(300 – 112000)
Platelets : median [range]	14500	(1000 – 332000)
Fibrinogen median (range)	196	(75–771)
PT median (range)	14.3	(11.8 – 30.6)
aPTT median (range)	27.2	(14.6 – 54.1)

*16 patients presented with low counts

APL Rxed …March 2011 to Feb 2017

Patient Characteristics	Number	
Total	53	
Gender (Male : female)	19/25	43.18%/56.81%
Age (years): range	9 to 67	Median 33 years
Risk Stratification	Sanz criteria -Low 2 (3.7%) -Intermediate 18 (33.9%) -High 33 (62.2%)	Vikram Mathews Criteria -Non High 12(22.6%) -High 41(77.3%)

Table 4: Prognostic Score of APL (Sanz Score) [9]

	Low Risk	Intermediate Risk	High Risk
Leukocytes/ µl	< 10,000	≤ 10,000	> 10,000
Platelets/ µl	> 40,000	≤ 40,000	

Grimwade D et al. Characterization of APL cases lacking the classic t(15;17): results of the European Working Party. Blood 2000;96:1297-1308.

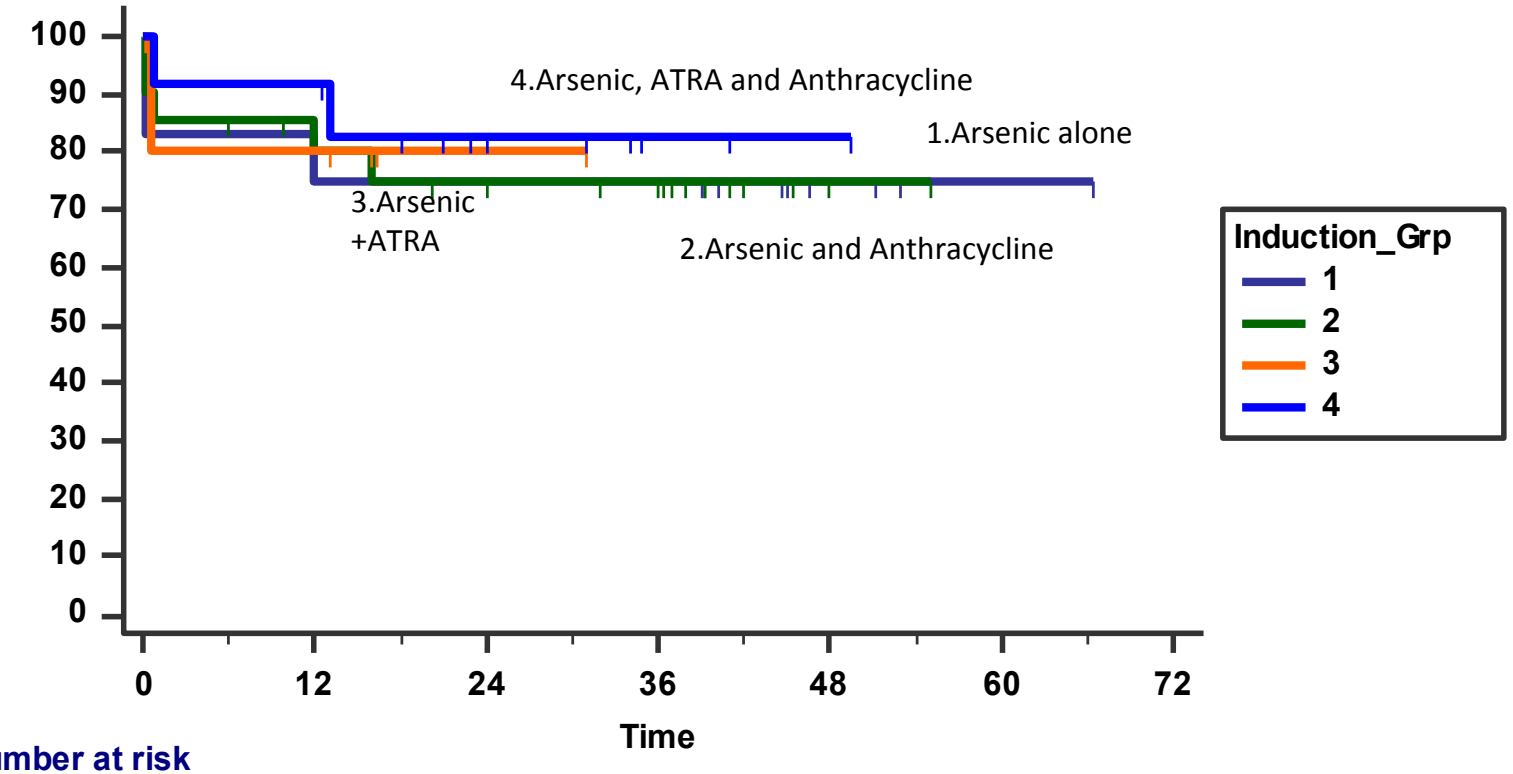
Vikram Mathew Criteria		
	High Risk	Non High Risk
TLC	>5000	<5000
Platelet	<20000	>20000

Mathews V et al. Single-agent ATO in the treatment of newly diagnosed APML: durable remissions with minimal toxicity. Blood 2006. 107: 2627-2632.

Treatment

PROTOCOL	Number (53)	Evalauble for Response (MR)	Induction deaths
Single agent Arsenic	12 (22.6%)	9/9	3
Arsenic + Anthracycline*	19 (35.8%)	18/18	1
Arsenic + ATRA	6 (11.3%)	6/6	
Arsenic and ATRA +Anthracycline	14 (26.4%)	13/13	1
Others (ATRA +Anthracycline)	2 (3.7%)	2/2	

RFS by Induction Treatment ….. 2017



Number at risk

Group: 1						
12	9	9	9	3	1	0
Group: 2						
21	15	12	10	1	0	0
Group: 3						
6	4	1	0	0	0	0
Group: 4						
12	11	6	2	1	0	0

Mortality Details

Patient	Age/Gender	Days from Induction	Cause of death	Risk stratification
1.	42/M	8 days	IC Hemorrhage	Intermediate risk
2.	24/F	19 days	IC Hemorrhage, Sepsis (GNB)	High Risk
3.	24/M	12months 15 days	Relapsed after 9 months, Sepsis (GNB and fungal infection)	High risk
4.	45/F	5 days	IC Hemorrhage	High risk
5.	16/M	4 days	IC Hemorrhage	High risk
6.	29/F	2 days	IC Hemorrhage	High risk
7.	46/F	25 days	Sepsis(GNB)	Intermediate risk
8.	29/M	8 days	Sepsis(GNB)	High Risk

Morbidity Details..

	Number
ICU	15 (28.3%)
Differentiation syndrome	23 (43.4%)
Infections	16 (30.2%)

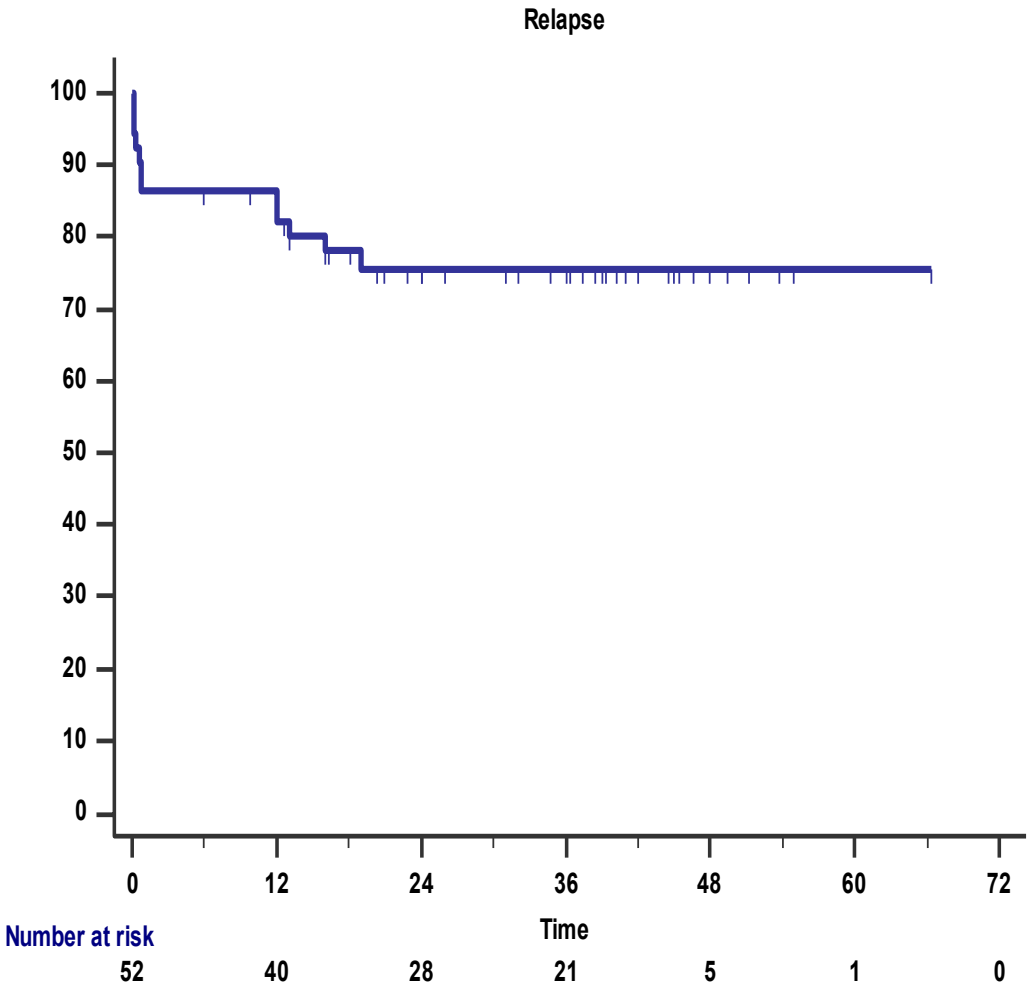
Supportive care….. For Rx of APL

	Mean and Range
Packed cells	4.8 (2 to 36)
Platelets (RDP)	17.2 (0 to 162)
SDP	1.6 (0 to 11)
FFP	6.8 (0 to 72)
Cryoprecipitate	10.8 (0 to 70)

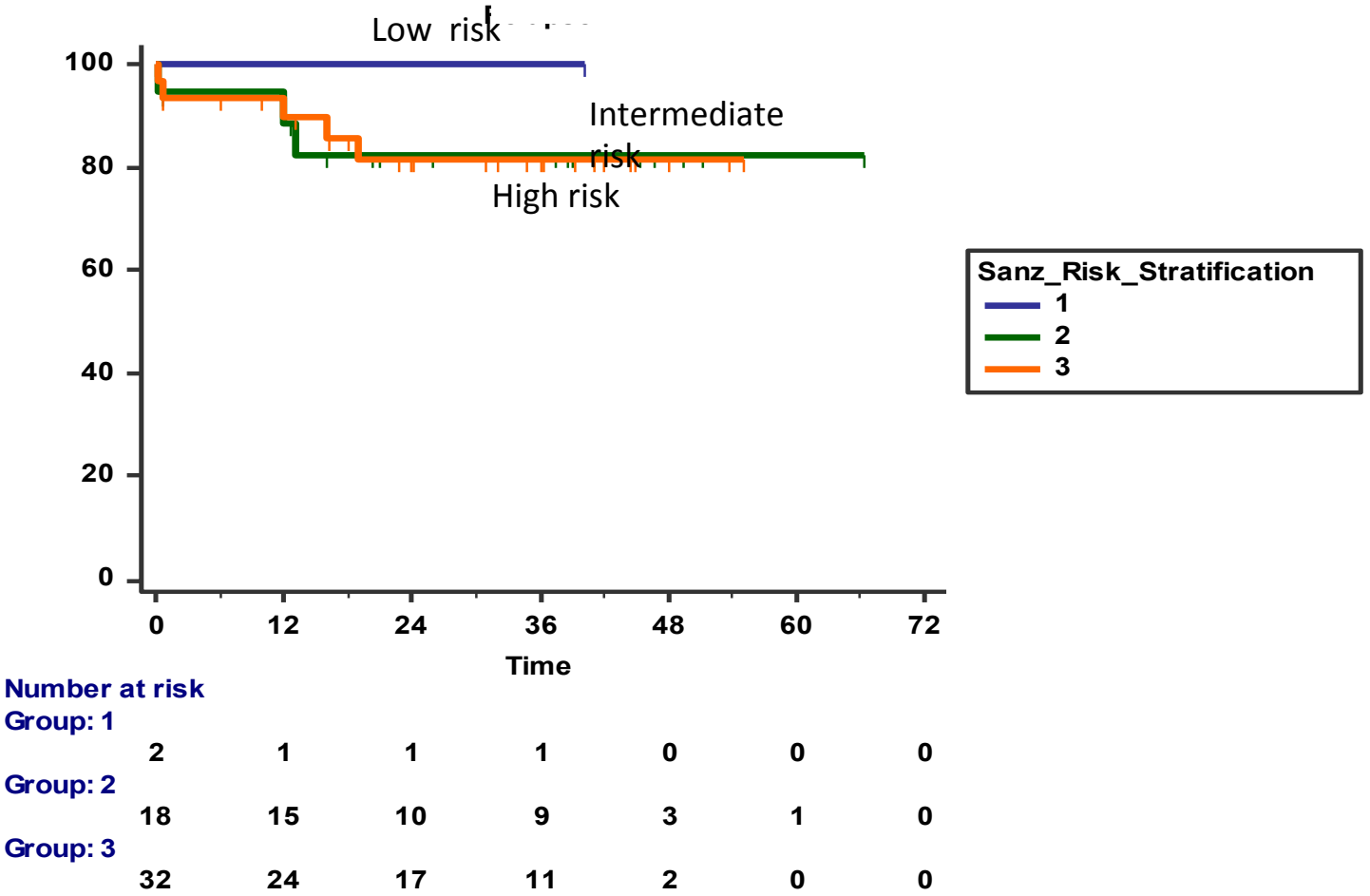
Status..... 2017

- Alive- 45/53 (85%)
- Dead : 8 [4- ICH, 1- ICH and infection, 3- infection]
- Relapse : 5 [Marrow-2, Marrow and CNS- 3]
- 1st Relapse salvaged- 3
- 2nd Relapse salvaged - 1

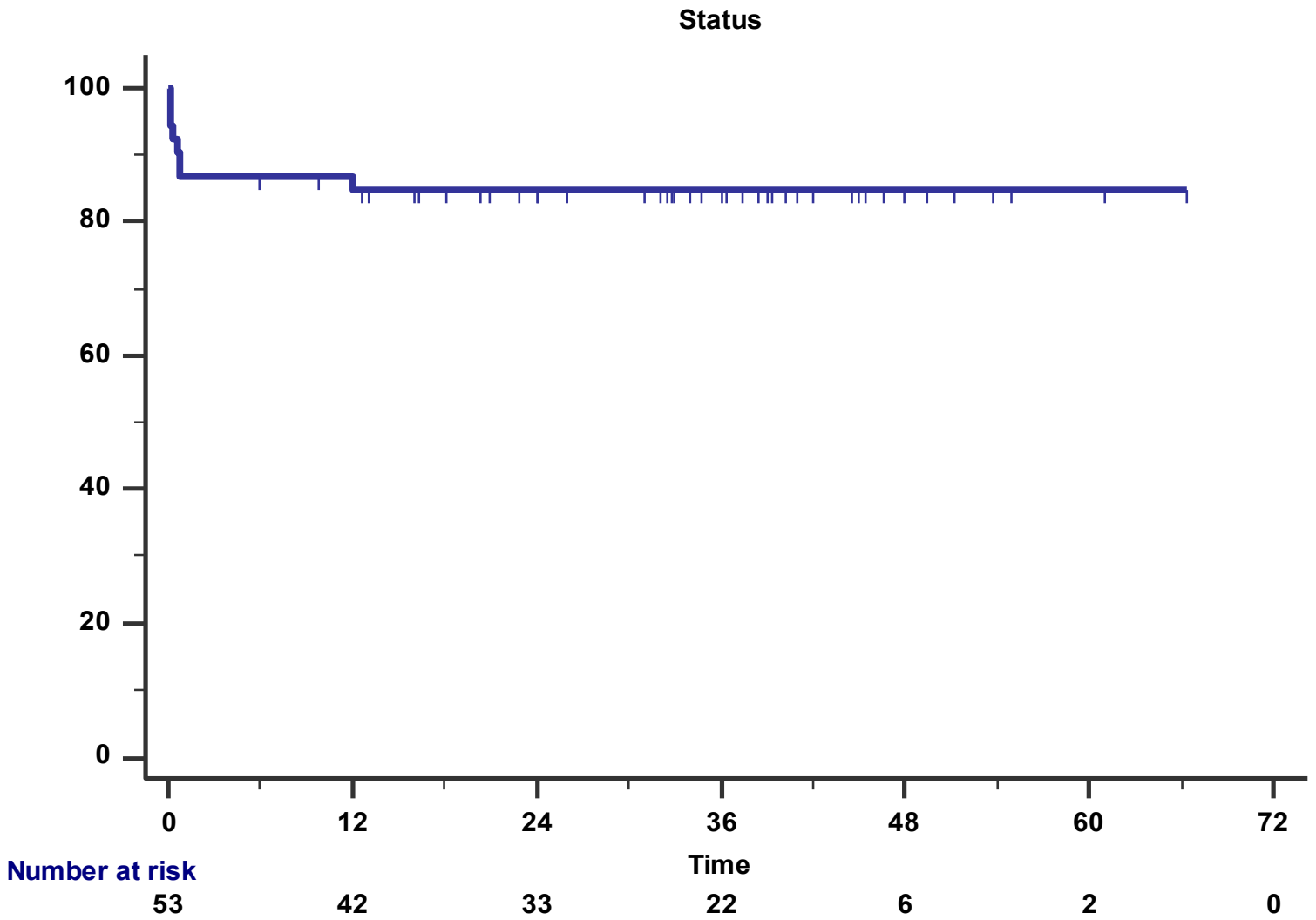
Relapse free survival …… 2017



Relapse Free survival.. APL 2011 to 2017



APL Overall survival……. Till 2017



Progress

For APL In India

India -Population profiles

- Profile I

AGE : 2 Years

FATHER: LABORER

MOTHER: LABORER

EDUCATIONAL STATUS: ILLITERATE

SIBLINGS: SIX

MONTHLY INCOME : US $ 200

70%

- Profile II

AGE : 5 YEARS

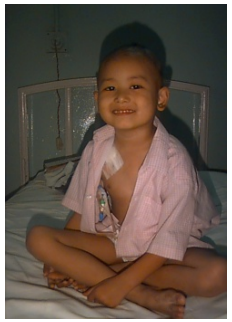
FATHER: BAKER

MOTHER: HOUSEWIFE

EDUCATIONAL STATUS : LITERATE

SIBLINGS : TWO

MONTHLY INCOME : US $ 200-1000



28%

Profile III

AGE : 10 YEARS

FATHER : BUSINESS

MOTHER : HOUSEWIFE

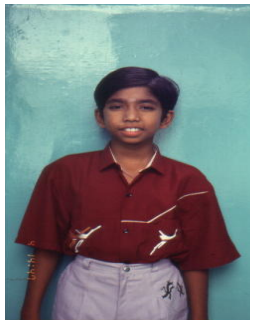
EDUCATIONAL STATUS

BOTH GRDUATES

SIBLINGS : ONE

MONTHLY INCOME

> US $ 3000 -?



2%

SOME DEMOGRAPHIC FEATURES OF USA & INDIA

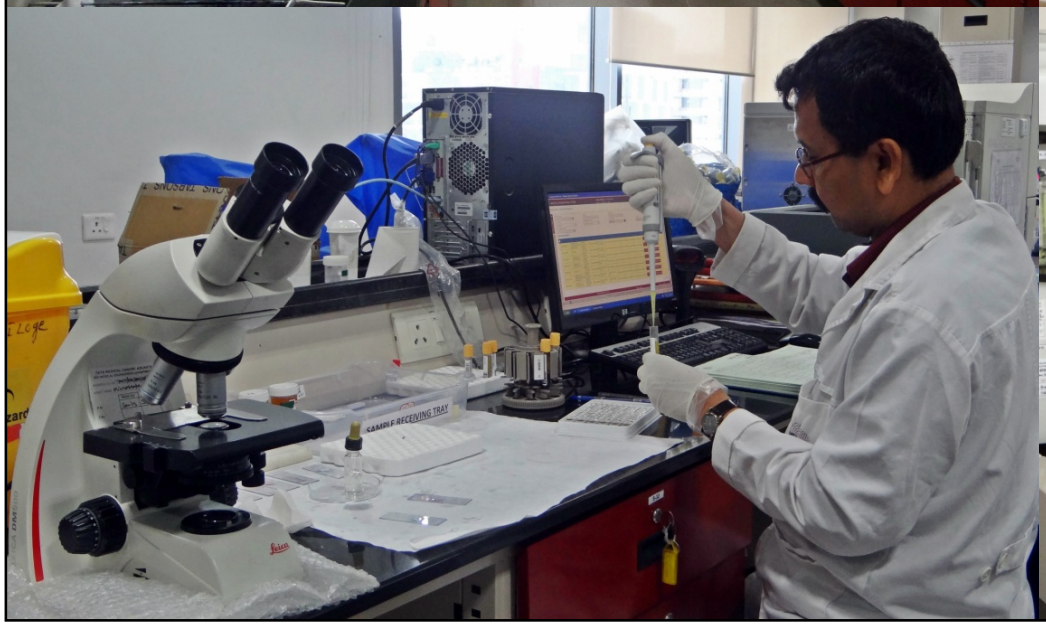
	USA -2017	**INDIA** 2013	**INDIA 2017**
POPULATION-m	362m	1.27 billion	1.35 billion
BIRTHS/1000	12	22	21
Deaths/1000	8	7	7
Infant Mortality	5.8	44	37
% Population<15	19	30	429
% Population >65	15	6	6
GNP/CAP- US$	58,030	**3840**	**6490**
Health Expend per Cap WB	8713	**15.82 (1995)**	**74.99 (2014)**

Data from: 2013 a& 2017 World Population Data Sheet, Population Reference Bureau, USA.

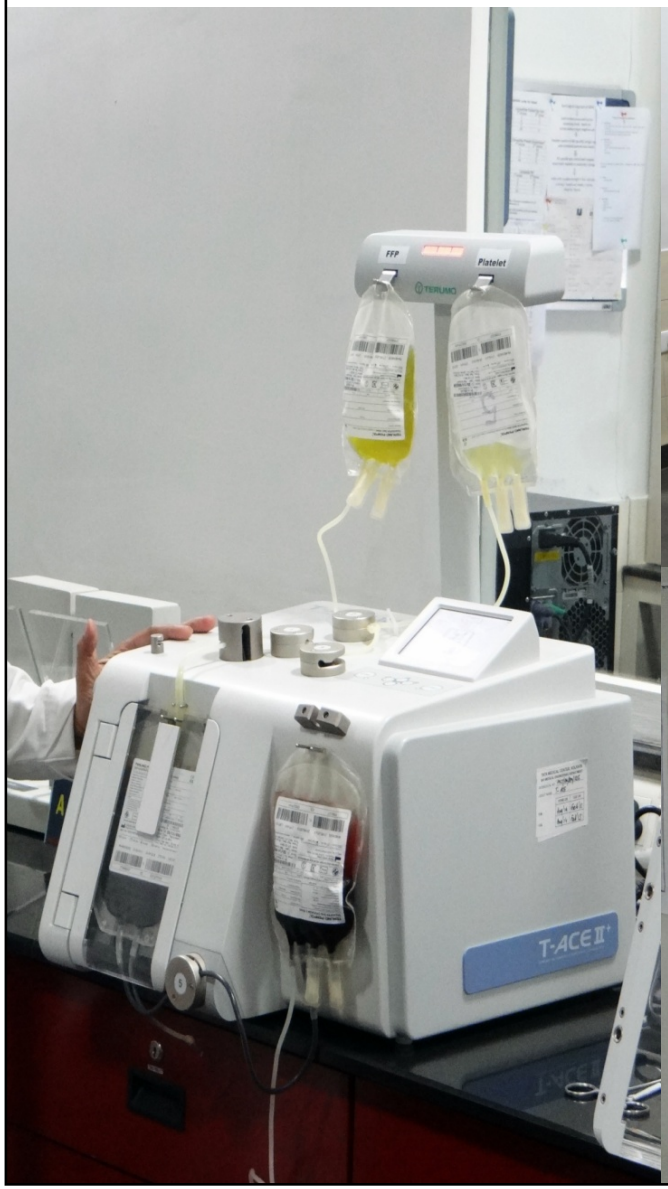
Progress

- For 30% of the population who can afford treatment for APL there is adequate infrastructure for treating APL
- Diagnostics: NABL accredited laboratories with quality control programs (national for coagulation, biochemistry, haematology)
- Blood components
- Molecular diagnostic facilities including FISH and RT-PCR.

DIAGNOSTIC LABORATORIES



Blood Components



MEDGENOME

With 5 Illumina HiSeq Next-Generation sequencing machines, MedGenome is the highest throughput NGS lab in South-East Asia

MEDGENOME

Analysis: Clinical Exome Sequencing Analysis Report

Fanconi anemia genes (*BRCA2, BRIP1, ERCC4, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, PALB2, RAD51C, SLX4*)

No significant variations were detected in Fanconi anemia genes.

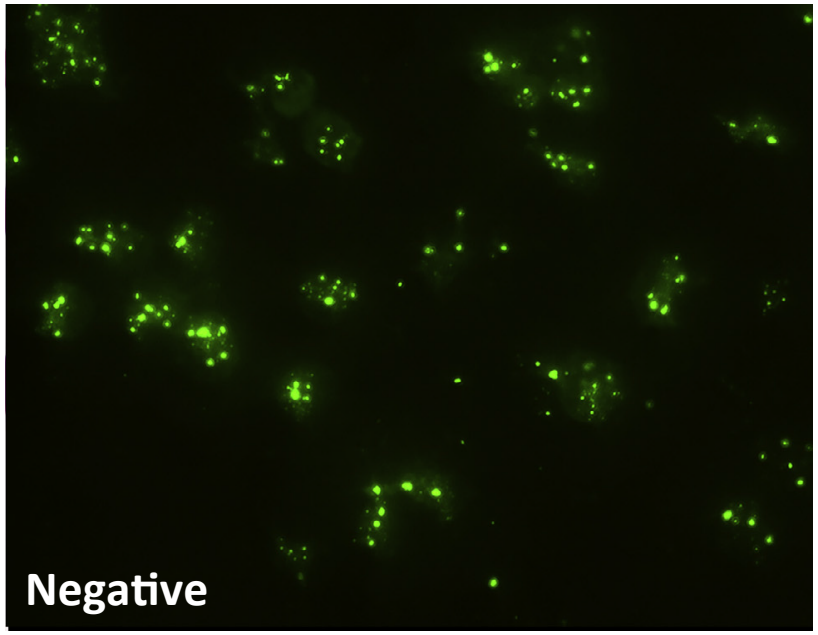
Table 3	Germline variations previously unreported for the phenotype and are of the type which may or may not be causative of the clinical phenotype					
S. No	Genomic Position	Gene Strand	Sequence Depth**	cDNA position #	Amino acid change	Exon no.
1	**chr12:49435968; G>G/A (HET)**	***KMT2D* (-)**	**108x**	**c.6013C>C/T (ENST00000301067)**	**p.R2005C**	**28**

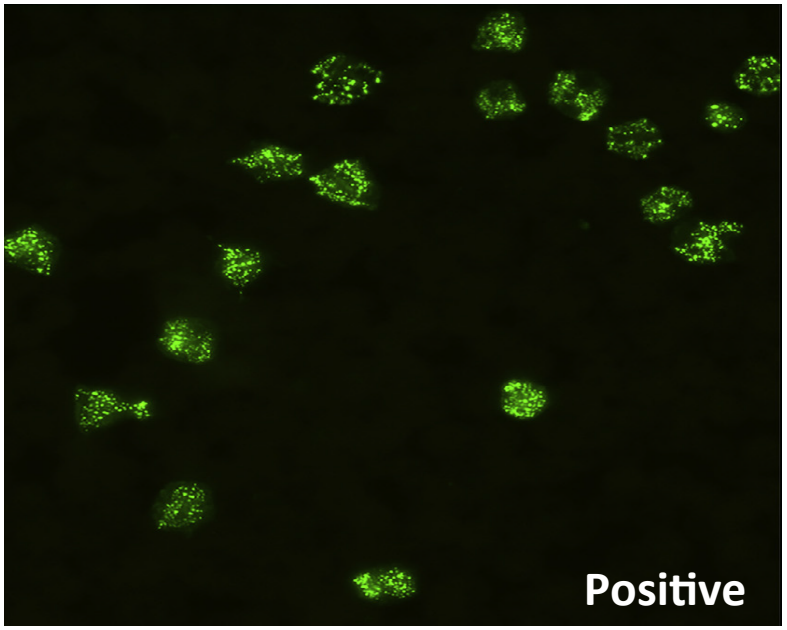
Should India rely on detection of PML by Immunofluorescence or cytochemistry for diagnosis of APML

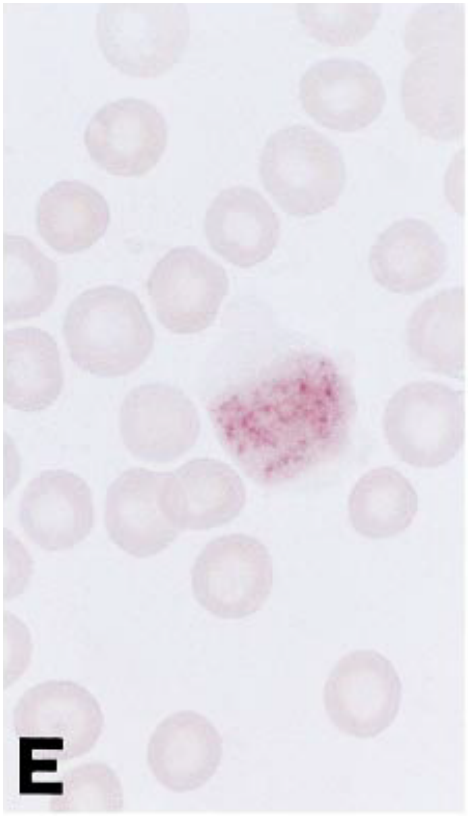
IF staining patterns

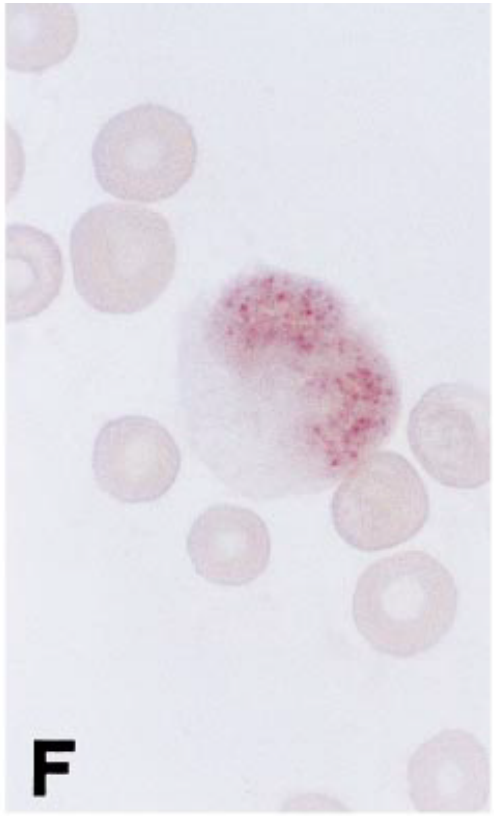
- In non-APL/ normal cells oncogenic domains can be observed as **5 to 30 intranuclear particles**

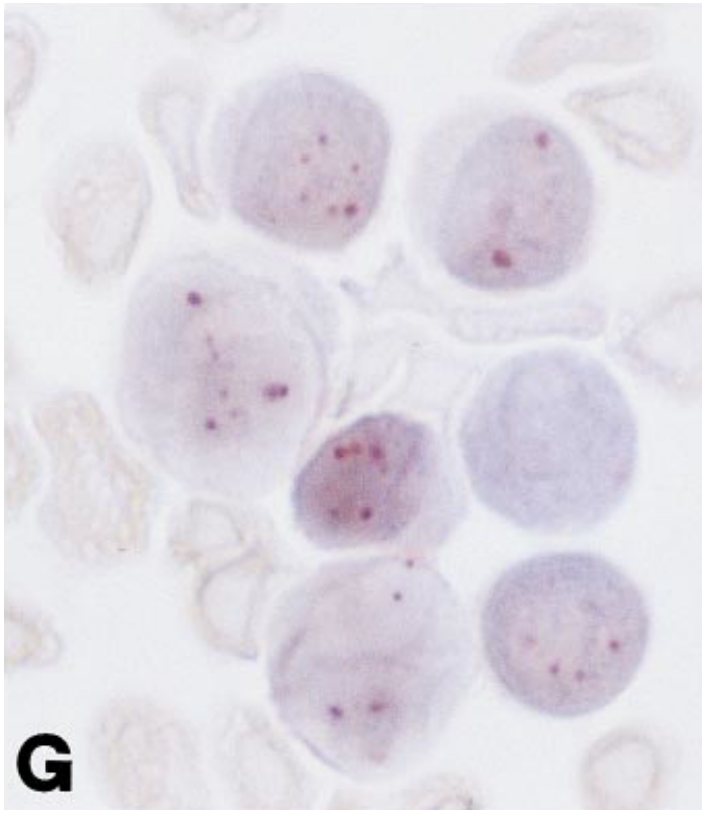
- In APL promyelocytes it is seen as a **microgranular nuclear pattern** of staining (due to formation of heterodimers between PML-RARa isoforms and PML protein)











typical micropunctate positivity of the PML/RARa fusion protein (APAAP technique; hematoxylin counterstain}

AML M5 typical speckled positivity of wild-type PML (APAAP technique; hematoxylin counterstain)

Literature review

S. No	Study	Number of cases* (APL/ non APL)	Positive IF pattern	Negative IF pattern	Comments
1	Falini B. et al. Blood 1997	92 (14/ 78)	14	78	100% concordance with RT-PCR results
2	Gomis F et al. Ann Hematol 2004	164 (110/ 54)	108^	54	
3	Dimov ND et al. Cancer 2010	349 (199/ 150)	196[#]	148[##]	Sensitivity 98.9%; Specificity 98.7%
4	Alayed KM et al. Arch Pathol Lab Med 2013	30 (9/ 21)	9	21	100% concordance with RT-PCR & FISH results

(*APL final diagnosis confirmed by RT-PCR for PML-RARα fusion)
([#]3 cases with PML-RARα fusion were missed in IF testing; [##]2 cases were falsely positive in IF testing)
(^2 cases - IF not worked due to scarcity of cells)

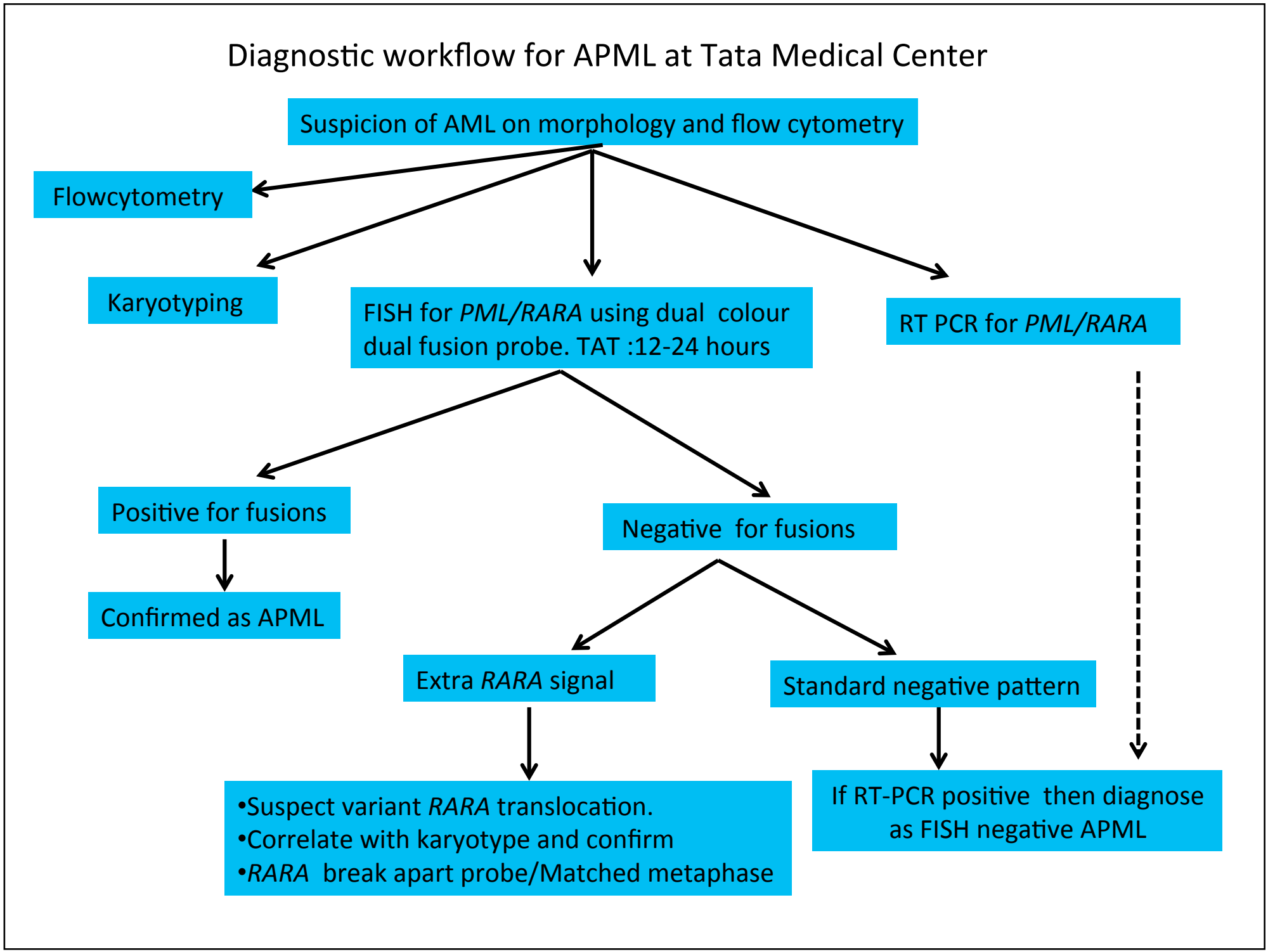
Advantages & Disadvantages

Advantages:

- Cheap **Cost $4**
- Less turnaround time (<4hrs)
- Can detect all types of fusion transcript (bcr 1, 2, 3) or cryptic translocations
- Technically less demanding in comparison to RT-PCR and FISH, more useful in clinical settings where cytogenetic and molecular testing are not readily available

Disadvantages:

- Microgranular pattern vs. nuclear bodies Interpretation can be difficult
- Has to be done on Fresh Sample
- Use in follow-up specimen not recommended
- Cannot be used in FFPE/ archival tissue specimens where there is increased possibility of false positive results
- Cannot detect variant *RARα* traslocations [t(11;17) etc.]


Diagnostic workflow for APML at Tata Medical Center
Suspicion of AML on morphology and flow cytometry
Flowcytometry
Karyotyping
FISH for PML/RARA using dual colour dual fusion probe. TAT :12-24 hours
RT PCR for PML/RARA
Positive for fusions
Negative for fusions
Confirmed as APML
Extra RARA signal
Standard negative pattern
•Suspect variant RARA translocation.
•Correlate with karyotype and confirm
•RARA break apart probe/Matched metaphase
If RT-PCR positive then diagnose as FISH negative APML

ARTICLE IN PRESS
Hematol Oncol Stem Cell Ther (2017) xxx, xxx–xxx
Available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/hemonc

CASE REPORT

Diagnosis of variant *RARA* translocation using standard dual-color dual-fusion *PML/RARA* FISH probes: An illustrative report

Manish Kumar Singh [a], Mayur Parihar [a,b,*], Neeraj Arora [b,c], Deepak Kumar Mishra [b,c], Saurabh Jayant Bhave [d], Mammen Chandy [d]

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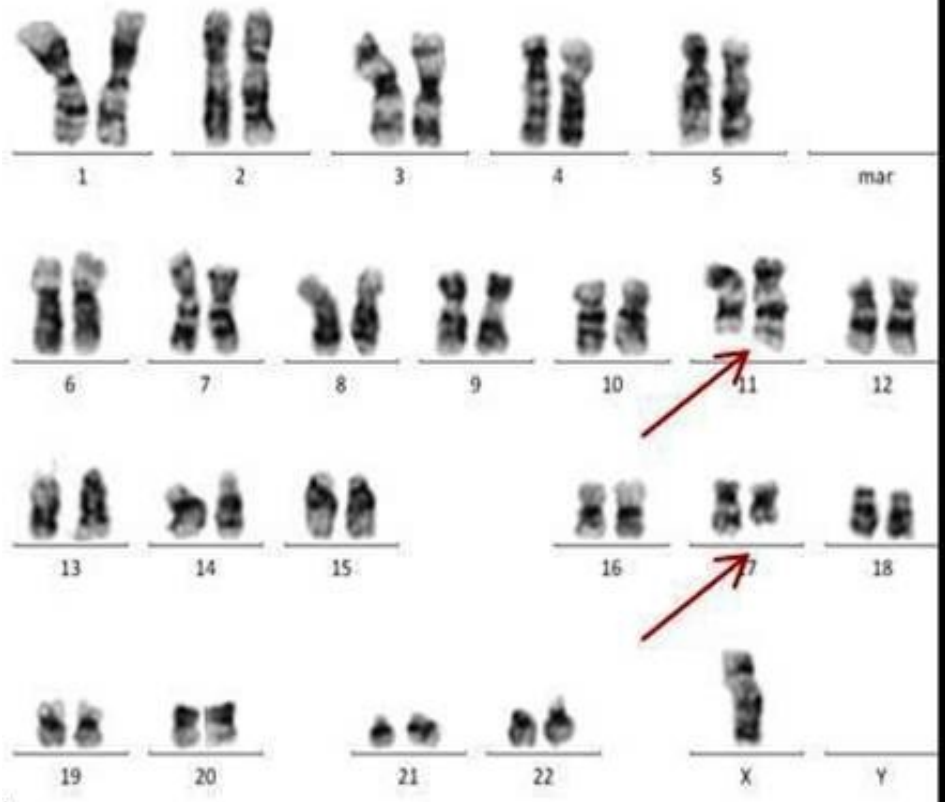
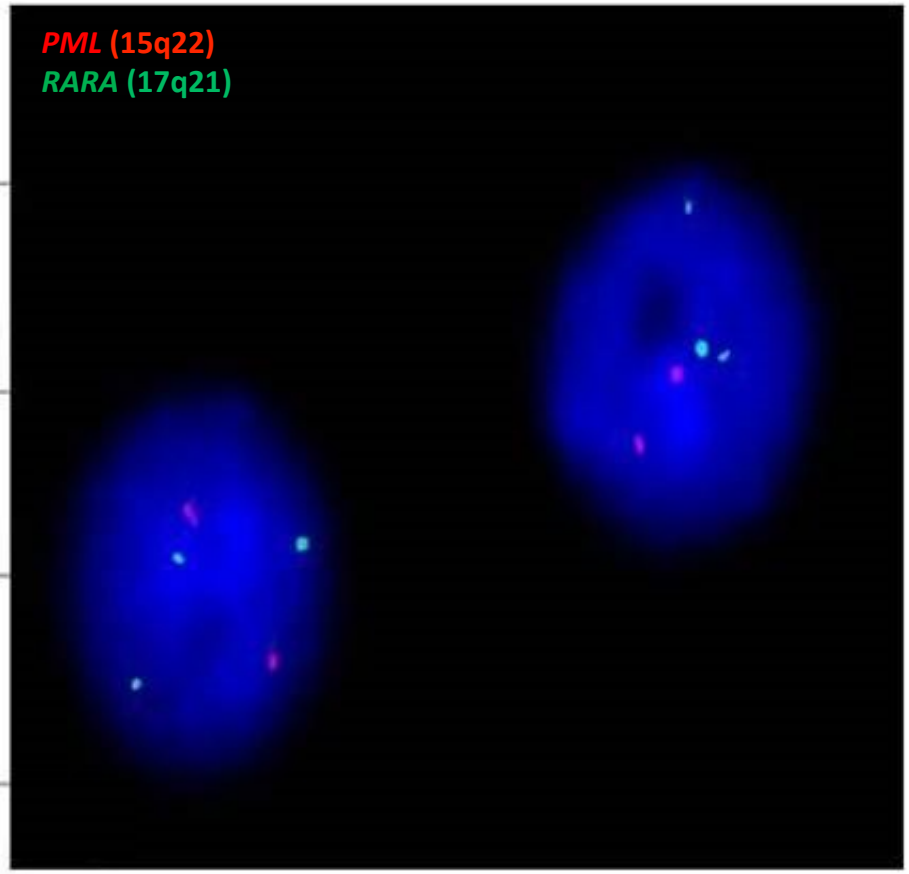
[b] Department of Laboratory Hematology, Tata Medical Center, Kolkata, India
[c] Department of Molecular Genetics, Tata Medical Center, Kolkata, India
[d] Department of Clinical Hematology, Tata Medical Center, Kolkata, India

Received 7 September 2016; accepted 25 December 2016

- 27/M, Referred from Bangladesh
- BM: s/o APML
- Started on ATRA, no response
- RT-PCR for *PML-RARA*: negative



46,XY,t(11;17)(q23;q21)[3]/45,idem,-Y[10]/46,XY[3]



FISH Negative RT-PCR Positive APML (6 cases in 5 years)

No.	Age	FISH FOR PML-RARa t(15;17)	Karyotyping	RT-PCR FOR PML-RARA(RNA)
UPN 1	28	Negative	46,XX[20]	POSITIVE (BCR1)
UPN 2	28	Negative	47,XY,+18[2]/46,XY[18]	POSITIVE (BCR1)
UPN 3	5	Negative	46,XY,der(10)t(10;?) (q25;?) [8]/46,XY,del(5)(q14) [1]/46,XY[11]	POSITIVE (BCR1)
UPN 4	4	Negative	Not done	POSITIVE (BCR1)
UPN 5	55	Negative	46,XY[20]	POSITIVE (BCR1)
UPN 6	10	Negative	Not done	POSITIVE (BCR1)

- All the above 6 cases had characteristic morphologic and flowcytometry findings of APML but were FISH t(15:17) negative and RT-PCR t(15:17) positive.

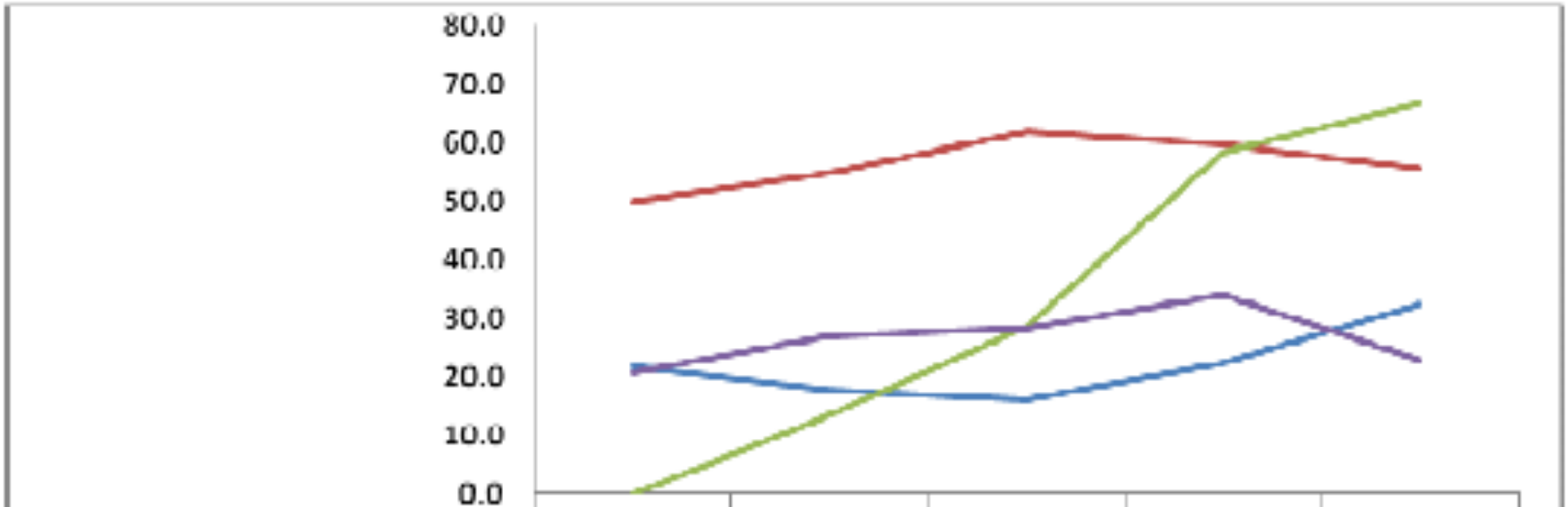
- FISH-negative cryptic PML-RARA rearrangement APML cases are rare
- Only 35 such cases described in the literature till date to be best of our knowledge (largest series is of 10 cases** with rest been case reports of one to three cases)

**Biomed Res Int 2013; 2013: 164501

Constraints

- Poor accessibility for good health care quickly for 70%
- Overburdened health care infrastructure
- Cost constraints within the government health care system
- Rising gram negative bacterial resistance

Carbapenem Resistance in Gram negative bacteremia



	2012	2013	2014	2015	2016
Carbapenem resistance in E. coli	22.0	17.8	16.3	22.5	32.3
Carbapenem resistance in Klebsiella spp.	50.0	54.7	61.7	59.7	55.5
Carbapenem resistance in Acinetobacter spp.	0.0	13.6	28.6	58.3	66.7
Carbapenem resistance in Pseudomonas spp.	20.8	26.9	28.3	34.0	23.0

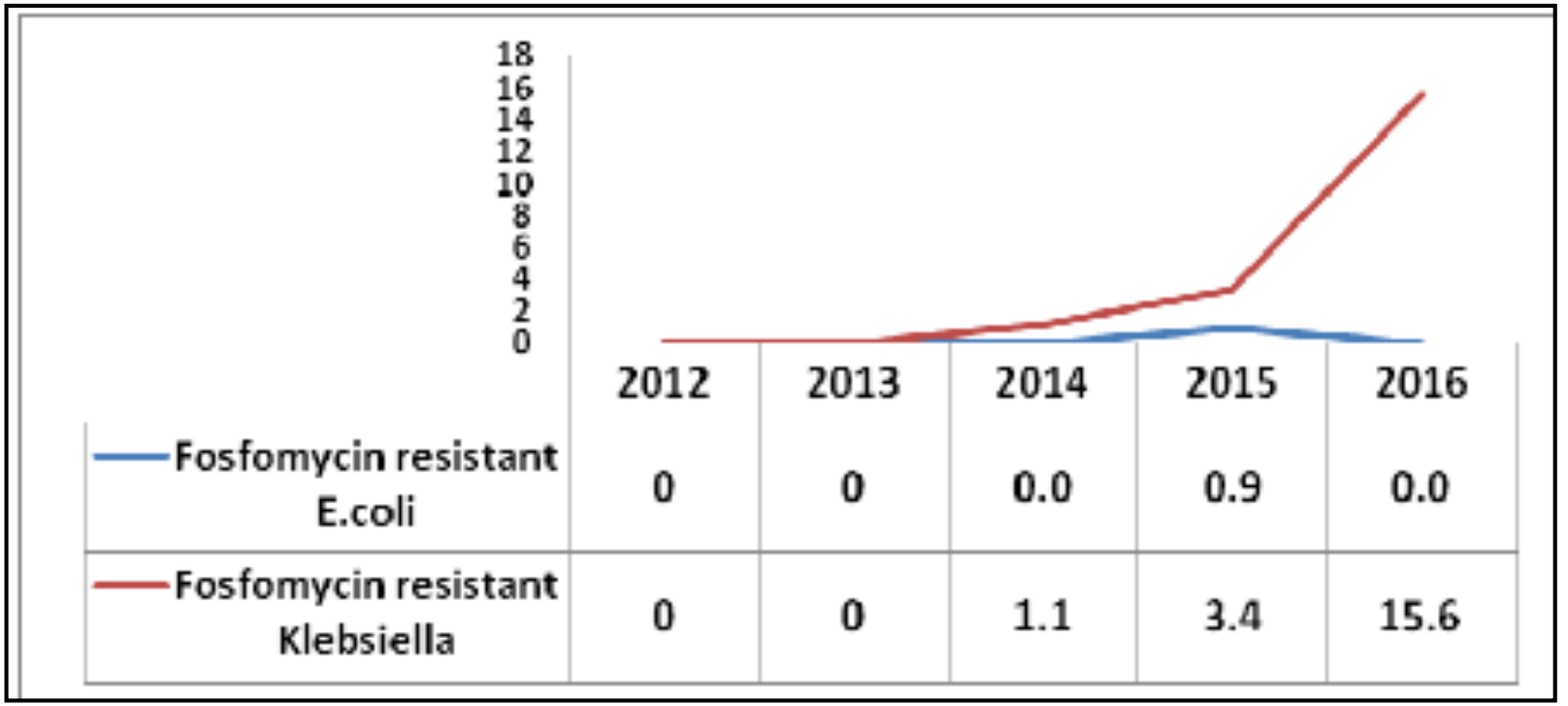
Carbapenem Resistance genes in E. coli and Klebsiella (all types of isolates- 2017)

Organisms (n)	Carbapenem Resistance genes detected by multiplex end point PCR: numbers (%)						
	KPC	NDM	IMP	VIM	OXA-48	NDM + OXA-48	NDM + VIM
E. coli (35)	–	20 (57.1)	–	–	5 (14.3)	5 (14.3)	1 (2.9)
Klebsiella sp (72)	2 (2.8)	9 (12.5)	–	–	39 (54.2)	17 (23.6)	1 (1.4)

Colistin Resistance in Gram Negative Bacilli (all sample types)

	2014	2015	2016
Organism	% colistin R	% colistin R	% colistin R
E coli	0.14	0.12	0.24
Klebsiella	1.98	2.60	3.12
Pseudomonas aeruginosa	0.00	0.00	0.87
Acinetobacter	0.00	0.00	4.49

Fosfomycin Resistance in Gram negative bacteremia



	2012	2013	2014	2015	2016
Fosfomycin resistant E.coli	0	0	0.0	0.9	0.0
Fosfomycin resistant Klebsiella	0	0	1.1	3.4	15.6

For India

- Baseline investigations: CBC, peripheral smear
- Doubt of acute leukemia: refer to tertiary center as emergency
- If morphology suggestive start treatment
- Bone marrow, Flow, cytogentics, FISH: if facilities available
- RT- PCR to referral center in PAX gene tube

RISK STRATIFICATION

- IC-APL (Sanz Criteria)

WBC count, × 10^9/L	183	3.6 (0.1–132)	
≤5			104 (57)
>5–10			21 (11)
>10–50			42 (23)
>50			16 (9)
Platelet count, × 10^9/L	183	23 (1–128)	
≤40			140 (77)
>40			43 (23)
Relapse-risk group	183		
Low			30 (16)
Intermediate			95 (52)
High			58 (32)

WBC < 10x 10^9/L no125 (68%)

- LoCoco: low and intermediate WBC<10x10^9/L
- Mathews:
  - Low risk (WBC) count lower < 5x10^9/L and platelet > 20x10^9/L
  - High Risk (WBC) >5x10^9/L and platelet < 20x10^9/L

- USE A SIMPLE CUTOFF OF 10,000 WBC TO DEFINE RISK

Choice of protocol

Choice of protocol in the developing world

- Simple and easy to administer
- Must be risk stratified
- Low risk of differentiation syndrome
    - Prevent with prednisolone (LoCoco NEJM)
    - Prevent with Hydroxyurea and treat with dexamethasone
- Low risk of grade ¾ neutropenia in consolidation
- Good outcome
- Low cost

Treatment with “standard” chemotherapy protocols without adequate support will result in a poor outcome

- Patient number: 134
- Treatment protocol: Anthracycline plus ATRA
- Induction mortality: 32.1%
- Bleeding as the cause of death: 60.5%.
- Mortality in consolidation: 10.5%
  - Bleeding:21.4%, infection: 28.6%, Both: 14.3%
- Cumulative mortality: 44.7%.

Jácomo RH et al Pagnano KB, Ribeiro R, Rego EM. Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica. 2007;92:1431-1432.

PETHEMA/HOVON LPA2005 Protocol

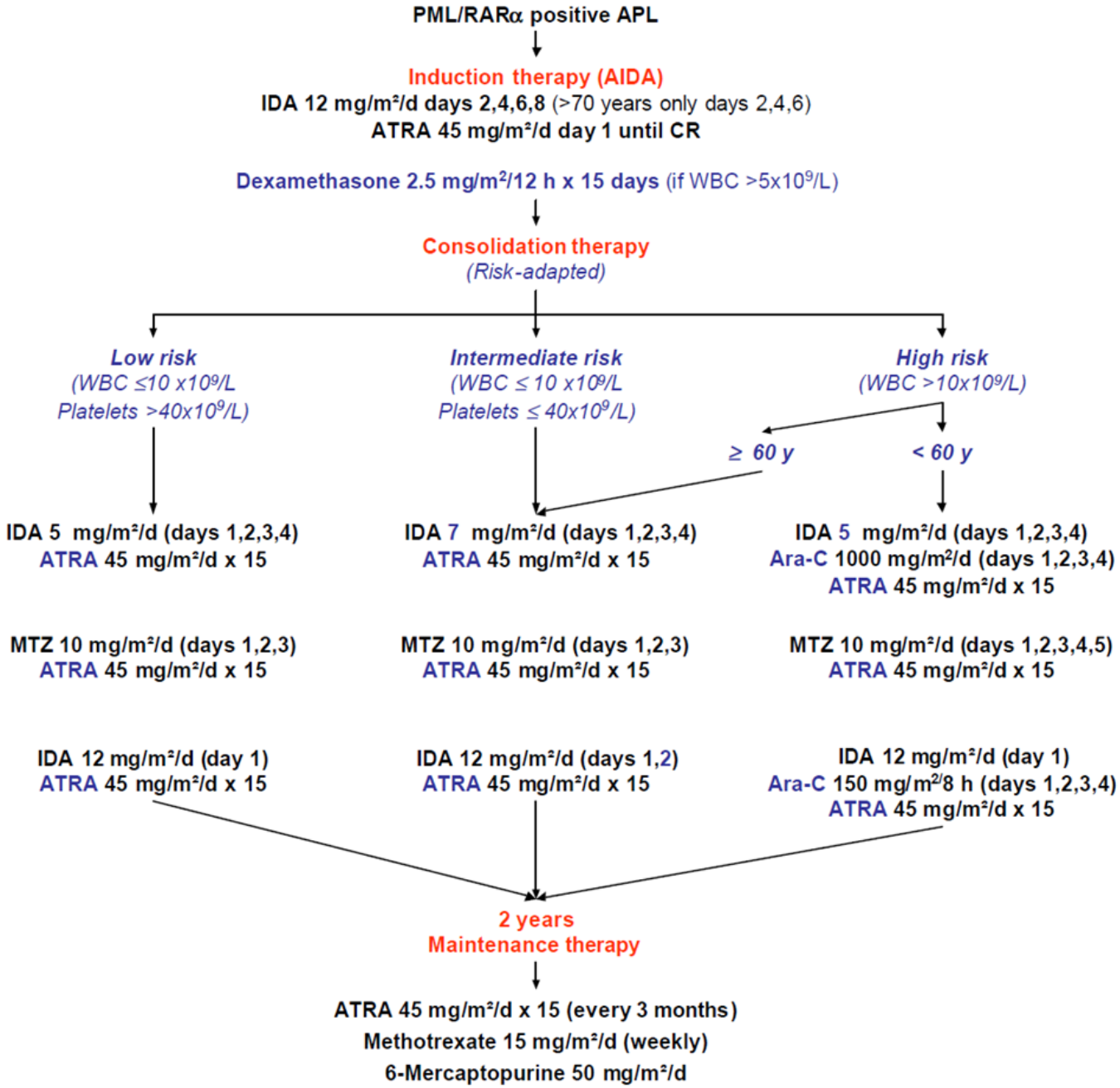


Table 1. Components of the APML4 protocol

Induction		
ATRA	45 mg/m^2/d PO	Days 1-36 in divided doses
Idarubicin	12 mg/m^2/d IV (ages 1-60) 9 mg/m^2/d IV (ages 61-70) 6 mg/m^2/d IV (ages > 70)	Days 2, 4, 6, and 8
ATO	0.15 mg/kg/d IV	Days 9-36 as a 2-hour IV infusion Supplemental potassium and magnesium as required to maintain serum levels in the upper half of the respective normal ranges
Prednisone	1 mg/kg/d PO	Days 1-10 or until WBC count falls below 1×10^9/L or until resolution of differentiation syndrome (whichever occurs last)
Hemostatic support	Products administered once or twice daily as required to achieve specified targets	Platelets > 30×10^9/L Normal prothrombin time Normal activated partial thromboplastin time Fibrinogen > 1.5 g/L
Consolidation cycle 1 (3-4 wks after the end of induction)		
ATRA	45 mg/m^2/d PO	Days 1-28
ATO	0.15 mg/kg/d IV	Days 1-28
Consolidation cycle 2 (3-4 wks after the end of consolidation cycle 1)		
ATRA	45 mg/m^2/d PO	Days 1-7, 15-21, 29-35
ATO	0.15 mg/kg/d IV	Days 1-5, 8-12, 15-19, 22-26, 29-33
Maintenance: 8 cycles (3-4 wks after the end of consolidation cycle 2)		
ATRA	45 mg/m^2/d PO	Days 1-14
MTX	5-15 mg/m^2/wk PO	Days 15-90
6MP	50-90 mg/m^2/d PO	Days 15-90

PO indicates oral administration.

***Harry J Iland Blood. 2012;* 120(8):1570-1580)**

Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity

Vikram Mathews, Biju George, Kavitha M. Lakshmi, Auro Viswabandya, Ashish Bajel, Poonkuzhali Balasubramanian, Ramachandran Velayudhan Shaji, Vivi M. Srivastava, Alok Srivastava, and Mammen Chandy

Figure 1. Regimen of single-agent arsenic trioxide. Arsenic trioxide was administered intravenously at a dose of 10 mg for adults and 0.15 mg/kg for pediatric patients until CR. Another 4-week course (consolidation) was administered after a 4-week interval for those achieving CR. Subsequently, after a second 4-week interval it was administered for 10 days/month for 6 months (maintenance).

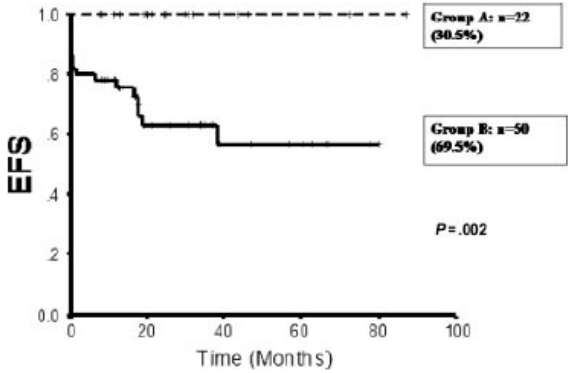
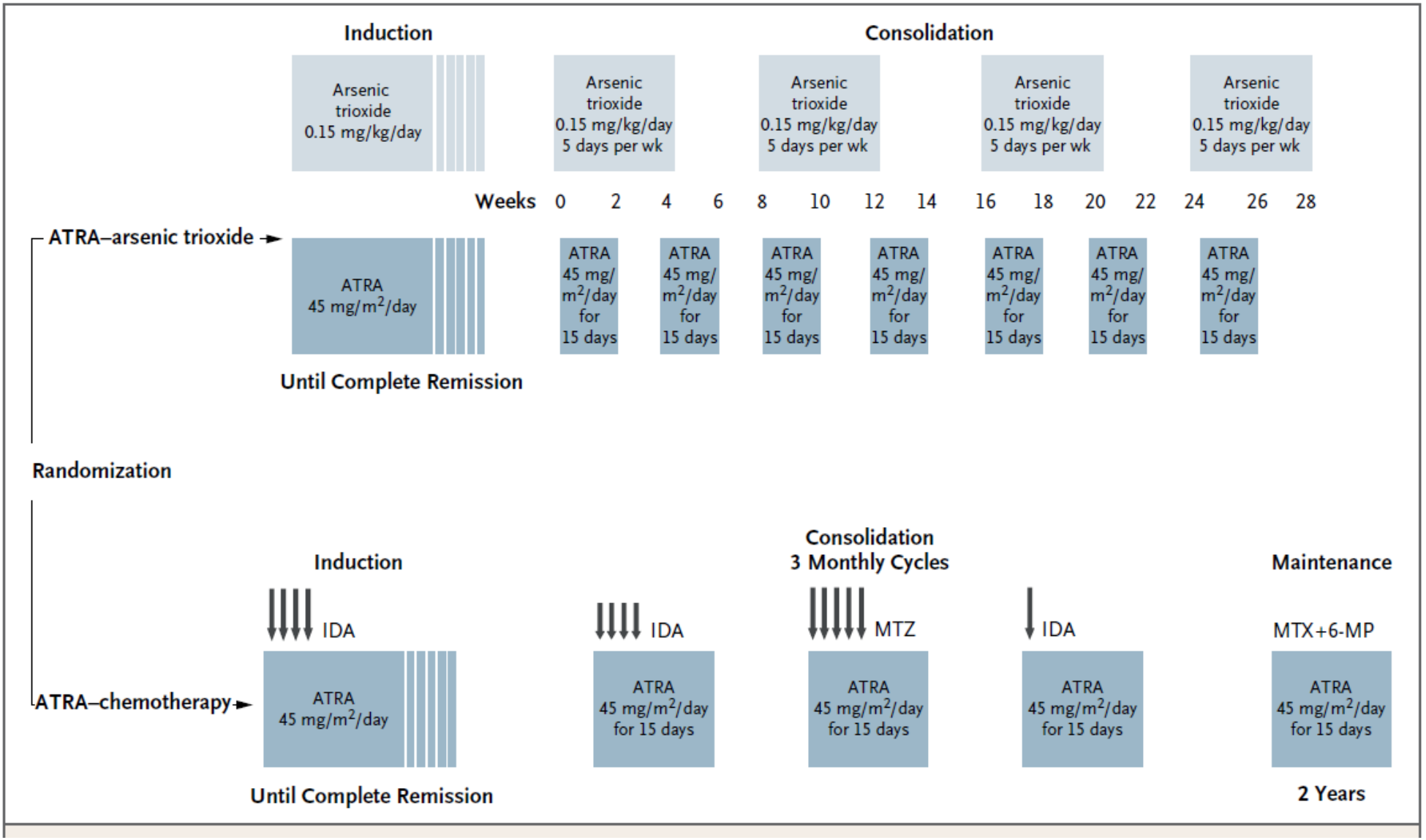


Figure 3. Comparison of Kaplan-Meier product limit estimate of event-free survival (EFS) between the good-risk group (group A: WBC count, $< 5 \times 10^9$/L; platelet count, $> 20 \times 10^9$/L) and the rest (group B).

Blood. 2006;107: 2627-2632


Induction
Consolidation
Arsenic trioxide 0.15 mg/kg/day
Arsenic trioxide 0.15 mg/kg/day 5 days per wk
Arsenic trioxide 0.15 mg/kg/day 5 days per wk
Arsenic trioxide 0.15 mg/kg/day 5 days per wk
Arsenic trioxide 0.15 mg/kg/day 5 days per wk
Weeks 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
ATRA–arsenic trioxide
ATRA 45 mg/m2/day
ATRA 45 mg/m2/day for 15 days
Until Complete Remission
Randomization
Induction
Consolidation 3 Monthly Cycles
Maintenance
IDA
MTZ
MTX+6-MP
ATRA–chemotherapy
ATRA 45 mg/m2/day
ATRA 45 mg/m2/day for 15 days
Until Complete Remission
2 Years

Prevention/RX of differentiation syndrome

- IC-APL: dexamethasone 10 mg IV twice daily
- Lo Coco NEJM

  Prednisone: 0.5 mg/kg/day - day 1 to end of induction.
  - Rx of differentiation syndrome, ATRA and/or arsenic trioxide temporarily discontinued: IV dexamethasone 10 mg q 12 h for 3 days or till resolution
- Mathews. Blood: Hydroxyurea/ Dexamethasone/ Anthracycline

Table 1. Guidelines for administration of hydroxyurea during induction

WBC count, $\times 10^9$/L	Adult patients	Pediatric patients
5 to 10	500 mg once daily	15 mg/kg once daily
10 to 15	500 mg twice daily	15 mg/kg twice daily
15 to 20	500 mg thrice daily	15 mg/kg thrice daily
20 to 50	500 mg 4 times a day	15 mg/kg 4 times a day
More than 50	1.0 g 4 times a day	30 mg/kg 4 times a day

For adult and pediatric patients with a WBC count less than 5 $\times$ 10^9/L, no hydroxyurea was administered.

ANTHRACYCLINE (mitoxantrone) administered if leukocyte count higher than 50 109/L at presentation or rapidly progressive leukocytosis defined as a rise higher than 30* 10^9/L in the first week or higher than 50 10^9/L in the second week

	PETHEMA-HOVON Lo Coco-NEJM	APML-4 Iland et al	SINGLE AGENT ARSENIC Mathews etal	ATRA+ ARSENIC Lo Coco-NEJM
Number	79	124	72	77
Low Risk%	0	26%	30.6% *	100
Remission %	95	95	86	100
Induction Mortality %	5	4	14	0
Differentiation Syndrome %	16	14	6.9	19
Neutropenia- gr4/5>15d	35/76/25	-/52/26	-/0	6/4/4
Relapse number/ %	6	4.5	10	1
OS	91	93.2	86	99
EFS/DFS/FFR	86	88.1/97.5	74/87	97

Time to hematologic remission

- Median time to hematologic complete remission
  - ATRA + ARSENIC: 32 days (22-68)
  - ATRA + CHEMOTHERAPY: 35 days (26-63)
  - ARSENIC ALONE: 42 days (24-70)

- SEQUENCE
  - Arsenic first followed by ATRA
  - Simultaneous
  - ATRA first followe by Arsenic

Cost of treatment

Chemotherapy costs

Supportive costs

Cost of agents used to treat APL

Generic Name	MRP in RUPEES	US$	International price US$
MITOXANTRANE -10mg	394	6	150
TRETINOIN 10 mg x 100 tab	8700	1.6	4
IDARUBICIN- 5 mg	7448	120	
ARSENIC TRIOXIDE 10mg	429	7	400

Comparative Drug cost

- **Arsenic + ATRA**
- Arsenic 10 mg RS 400 $400
  - Induction: 32 vials
  - Consolidation: 80 vials
  - Total: 112 vials
  - Cost
    - INR RS 44,800 ($1400)
    - International $ 45,000
- ATRA 10 mg RS 100 $4
  - 10mgx7/day x 140 days
  - 1000 tab of10 mg @RS 100/ tab
  - Cost
    - INR RS 100,000
    - USD 4000

- **Single agent Arsenic**
- Arsenic 10 mg RS 400 $400
  - Induction: 42 vials
  - Consolidation: 30 vials
  - Maintenance: 60 vials
  - Total: 132 vials
  - Cost
    - INR RS 52,800 ($800)
      International: $ 53,800

- **Arsenic + ATRA + Idarubicin**
  - Idarubicin 16x5 mg: Rs 120000
  - ATO 80x 10 mg: Rs 32,000
  - ATRA 1400 x 10mg: Rs 140,000
  - TOTAL : 2,92,000
- India $ 5000
- International: $53,600

Comparative cost

- Arsenic alone Mathews
  - India price: RS 100,000 ($1600)
  - International price : RS 3,338,000 ($53,800)
- Arsenic + ATRA LoCoco
  - India price: RS 184,000 ($ 3100)
  - International price: RS 2,940,000 ($49,000)

CHOICE OF PROTOCOL FOR THE DEVELOPING WORLD

- Low risk
  - Single agent arsenic

    OR
  - Arsenic + ATRA
- Intermediate and High risk
  - Arsenic + ATRA + anthracycline
  - (mitoxantrone/daunorubicin)

Thank you