Outcome of acute promyelocytic leukemia patients Experience of Children Welfare Teaching Hospital (2010-2015) Baghdad/Iraq

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7° International Symposium on Acute Promyelocytic Leukemia

Rome, September 24 – 27, 2017

Rationale

- Before Sep. 2003, No specific APL protocol was employed
- Induction consisted of ARA-C + Anthracycline **(ATRA was not available)**
- Prognosis was poor with a high induction fatality of > 70% due to hemorragic events
- A study of 31 patients; induction mortality was 79%, CR 16%, and only 1 patient remained in CCR at 5y.

A Nostalgic email on June 29, 2017

- Hi sir,i was searching about any contact that i can reach you and i would say thank you so much for your efforts that u did to me and i am very glad that i found your email that i can contact you ..
- I will be very grateful if you give the email of dr.salma alhadad
- Thanks and very very hot regards from my family and I to you
- **((I was the 7 years old kid I came to your hospital in 2001 that I was diagnosed with high grade leukemia))**
- ((The pharmacist:-ahmed ismail)

ımed Albasha <a_albasha52@yahoo.com>
o: mazinaljadiry@yahoo.com

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I be very grateful if you give the email of dr.salma alhada
anks and very very hot regards from my family and I to yo
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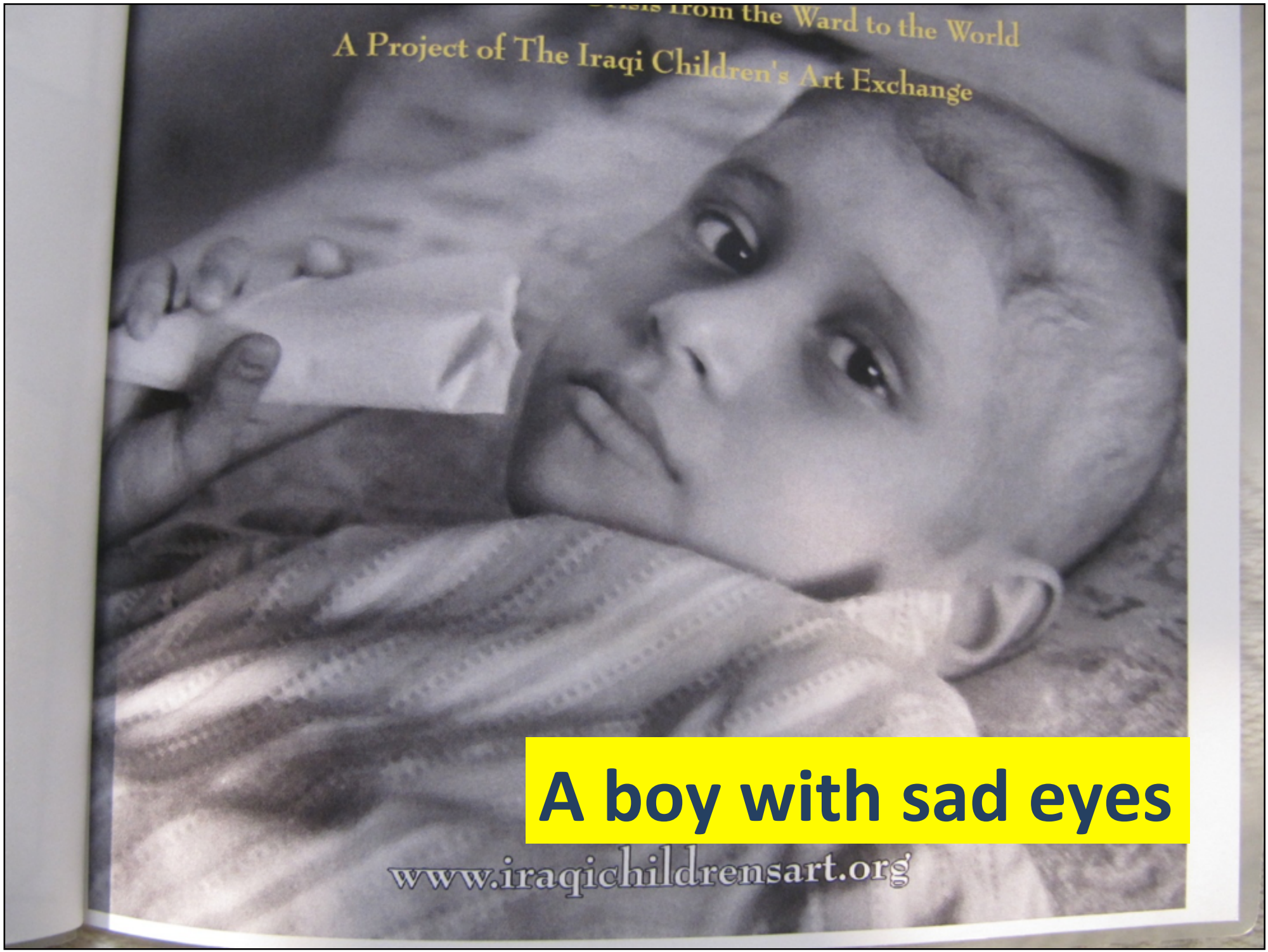
(The pharmacist:-ahmed ismail)

The only survivor

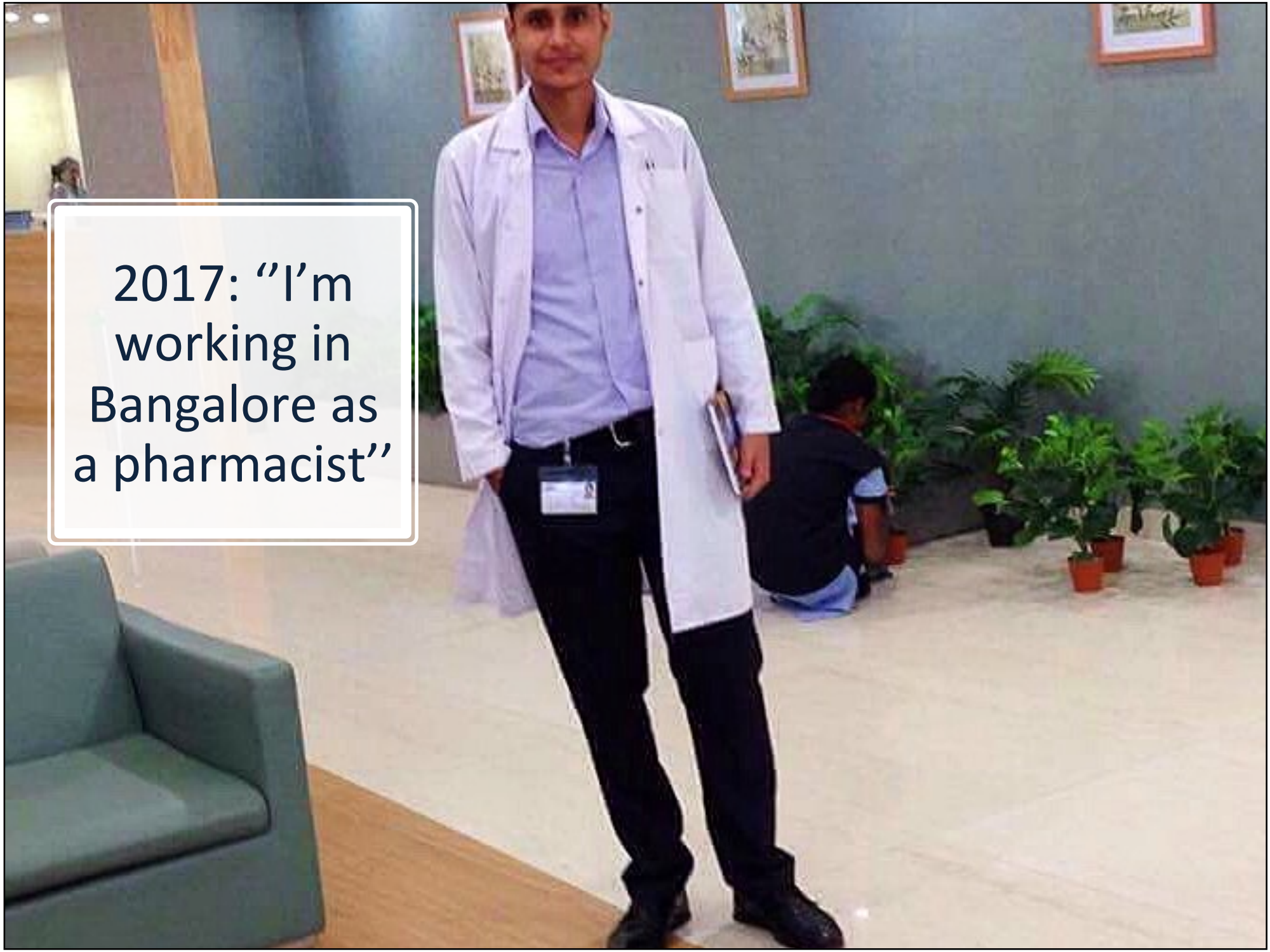
- Seven-year old boy
- Baghdad 2001-Sanction
- ATRA not available
- Started on chemotherapy for AML


from the Ward to the World
A Project of The Iraqi Children's Art Exchange
A boy with sad eyes
www.iraqichildrensart.org

In 2001

ATRA =Star trek

An American science fiction TV series
1966


2017: ‘’I’m working in Bangalore as a pharmacist’’

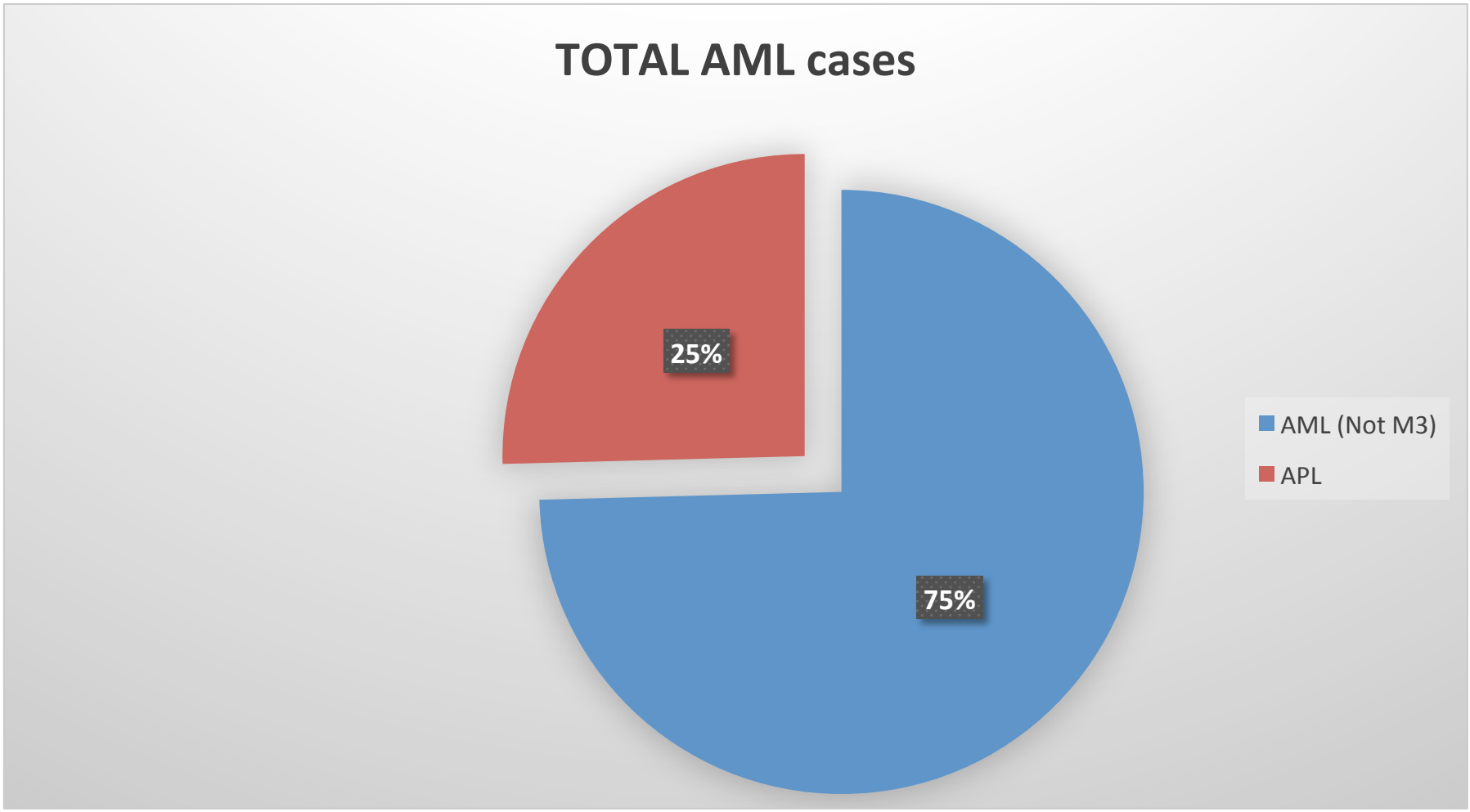
Email on Sept. 25, 2017

- Email was sent to Ahmed to find a way to buy ATRA and ATO for the children affected with his previous disease.

APL 2010-2015

- A retrospective descriptive study
- All patients are less than 14-year-old
- Jan.1, 2010 till Dec. 3, 2015
- From 181 De novo AML patients, APL diagnosed in 46 patients which constituted 25.4%.

Total number of cases over 6 years



Diagnostic challenges

- Morphology at CWTH:
  - One patient: only PBF (Diluted bone marrow for 3 times).
  - 45 patients: BMA
- No FCM or FISH
- Assisted Diagnostics:
  - 10 patients: S/R of morphology via telemedicine with Sapienza University.
  - 10 patients: BMA slides & FTA card shipped to shinshu university/Japan, by confirming the presence of PML-RARA transcripts obtained by nested RT-PCR, FISH was performed on BMA smears stained with May-Grünwald-Giemsa.

September 2003:

ATRA-based APL protocol

adapted to severe Iraqi difficulties

CWTH

Pediatric Hematology Units

Sapienza University of Rome- Medical City Baghdad

2006

Telemedicine Project

A second review of BM slides and follow up of APL cases

Nino Sergi

Anna Maria Testi

Team of Telemedicine Program

Angelici Alberto

Their work have made a substantial impact

Robin Foà

Luisa Moleti

Stefania Uccini

Alessandro Guarino

Carlo Domenici

APL Iraqi Protocol

	Amended version	
	Oct. 2009- till now	
Induction	ATRA 25 mg/m^2/day x 30 days +DNR	
Risk groups	SR (WBC<10,000)	HR(WBC≥10,000)
Consolidation 1	DNR +ATRA	DNR+ATRA
Consolidation 2	DNR+LD-CA+ATRA	DNR+LD-CA+6-TG+ATRA
Consolidation 3	DNR+ATRA	MTZ+VP16+ATRA
Maintenance	ATRA + MTX + 6MP	

Patients Characteristics

Total	46
Gender (M/F), ratio	21/25, 0.8:1
Age; median (min–max)	9.1 yr (9m -14.2yr)
WBC x 10^9/l; median (min-max)	5 (1-236)
Pltc- x 10^9/l; median (min–max)	15 (3-115)
Risk-gp; WBC at Dx. (SR/HR)	[28(61%)/18(39%)]

Induction phase

Status	No. (%)
Pre-Induction	**46(100)**
Refused treatment	2 (4.3)
Died before induction	3(6.5)
Evaluable for induction	**41(100)**
Induction death*	8/41(19.5)
Alive CR Not assessed	33/41(80.5) 32 1

*Death within 30 days from starting induction

Timing of ATRA after admission

- ATRA used on clinical suspicion/PBF without waiting the BM results
- Duration between admission & ATRA intake:
  - During 1st 24 hours: 25 patients
  - After 24 hours: 16

Characteristics of Very Early Deaths*

No.	Days since Dx.	Age/y	Subtype	Gender	Risk group	Mx	Cause of death
1	0	10	M3v	F	HR	**Supportive only**	ICH
2	2	3	M3v	M	HR	**Supportive only**	ICH
3	2	13	M3v	M	LR	**Supportive only**	ICH
4	3	5	M3	F	HR	ATRA+Chemo	ICH
5	3	10	M3	F	LR	**ATRA only****	ICH
6	4	1	M3v	M	HR	ATRA+ Chemo	**DS**
7	4	2	M3v	F	LR	ATRA+Chemo	ICH
8	5	4	M3	M	HR	ATRA+Chemo	ICH
9	5	11	M3	M	LR	**ATRA only****	**DS**

Median time since diagnosis: 3 days, 0-5 days

*Deaths within 7 days from diagnosis

**The child was started on ATRA on clinical suspicion/PBF before having BMA result

No ICU, No proper assessment for coagulation profile, No FCM to make a diagnosis

Characteristics of Early Deaths*

No.	Days since Dx.	Age/y	Subtype	Gender	Risk group	Mx	Cause of death
1	0	10	M3v	F	HR	**Supportive only**	ICH
2	2	3	M3v	M	HR	**Supportive only**	ICH
3	2	13	M3v	M	LR	**Supportive only**	ICH
4	3	5	M3	F	HR	ATRA+Chemo	ICH
5	3	10	M3	F	LR	**ATRA only****	ICH
6	4	1	M3v	M	HR	ATRA+ Chemo	**DS**
7	4	2	M3v	F	LR	ATRA+Chemo	ICH
8	5	4	M3	M	HR	ATRA+Chemo	ICH
9	5	11	M3	M	LR	**ATRA only****	**DS**
10	21	7	M3v	M	HR	ATRA+Chemo	Sepsis
11	29	10	M3v	F	HR	ATRA+Chemo	Sepsis

*Deaths within 30 days from diagnosis

Post Induction phases

Status	No. (%)
Post induction results	**33 (100)**
Abandoned before assessing BM	**1(3)**
CCR	**25(75.7)**
Relapse	**7(21.2)**
Died in CR	**0**

Relapsed patients 7

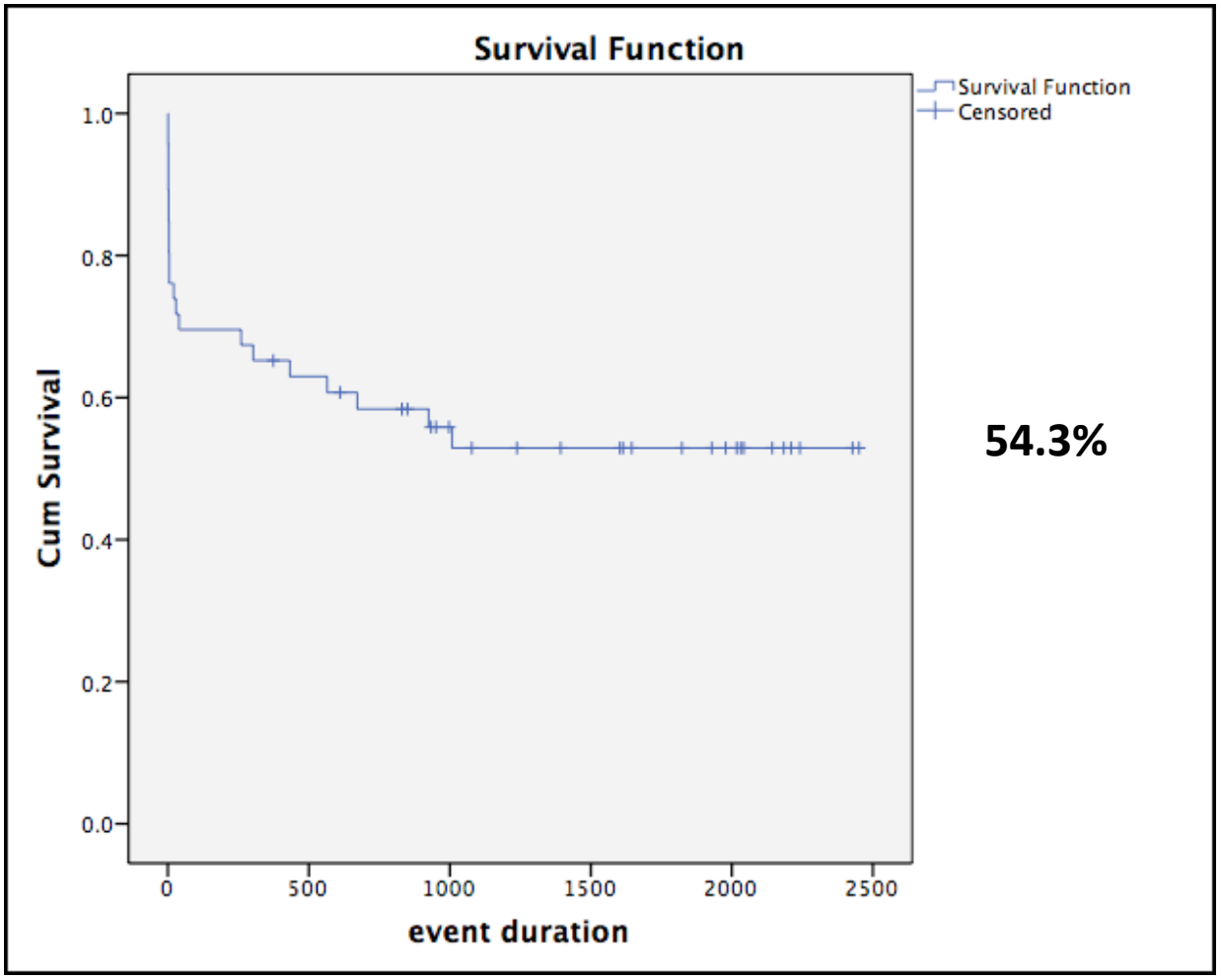
- 6 patients died:
  - 2 patients before reinduction
  - 4 patients during reinduction
- 1 still alive after receiving salvage therapy with MTZ & ARA-C

Fate of relapsed patients

N.	Months since Dx.	Age	G	subtype	Risk gp	Action	Days between R. & Last F.up	Fate
1	19	1	F	M3V	HR	Chemo.	24	Died
2	9	7	F	M3V	LR	Chemo	29	Died
3	23	13	M	M3	LR	Supportive	5	Died
4	34	10	F	M3	LR	Chemo	45	Died
5	15	8	F	M3	HR	Chemo	0	Died
6	31	9	M	M3	LR	Chemo	942	Alive
7	11	7	M	M3	LR	Supportive	9	Died

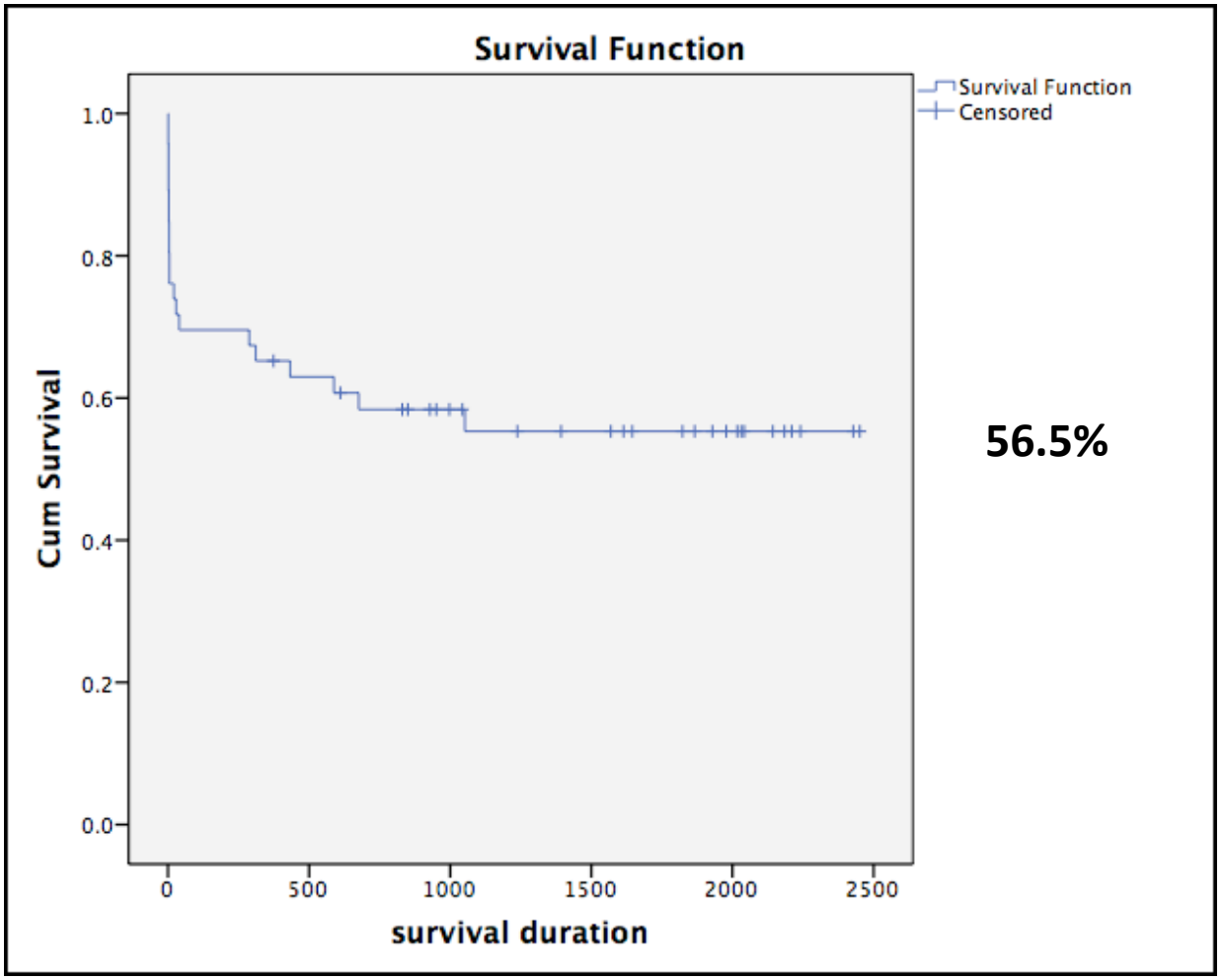
Median since diagnosis was 19 months (range 9-34 months)

Event Free Survival of 46 APL patients



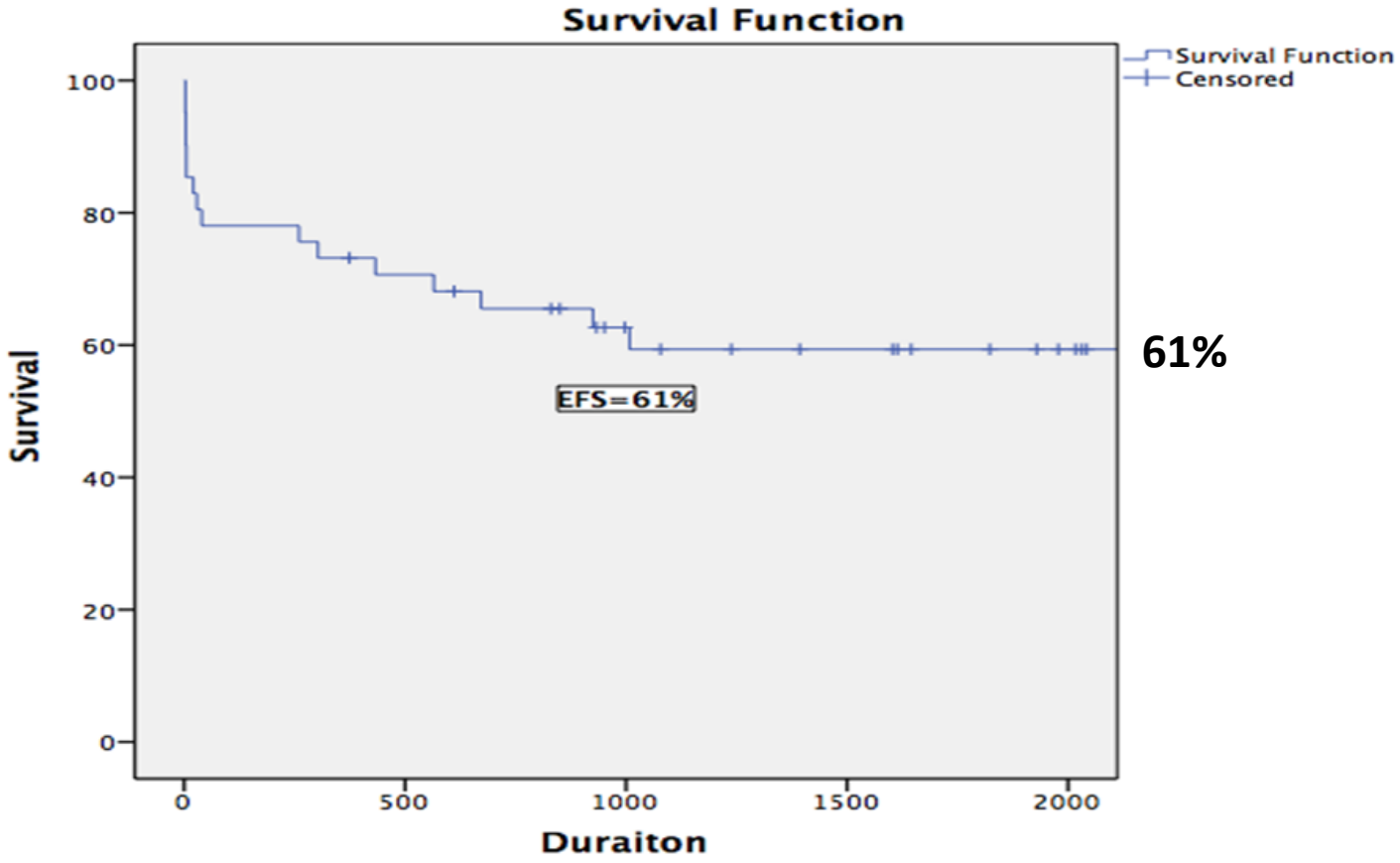
54.3%

Overall Survival of 46 APL patients



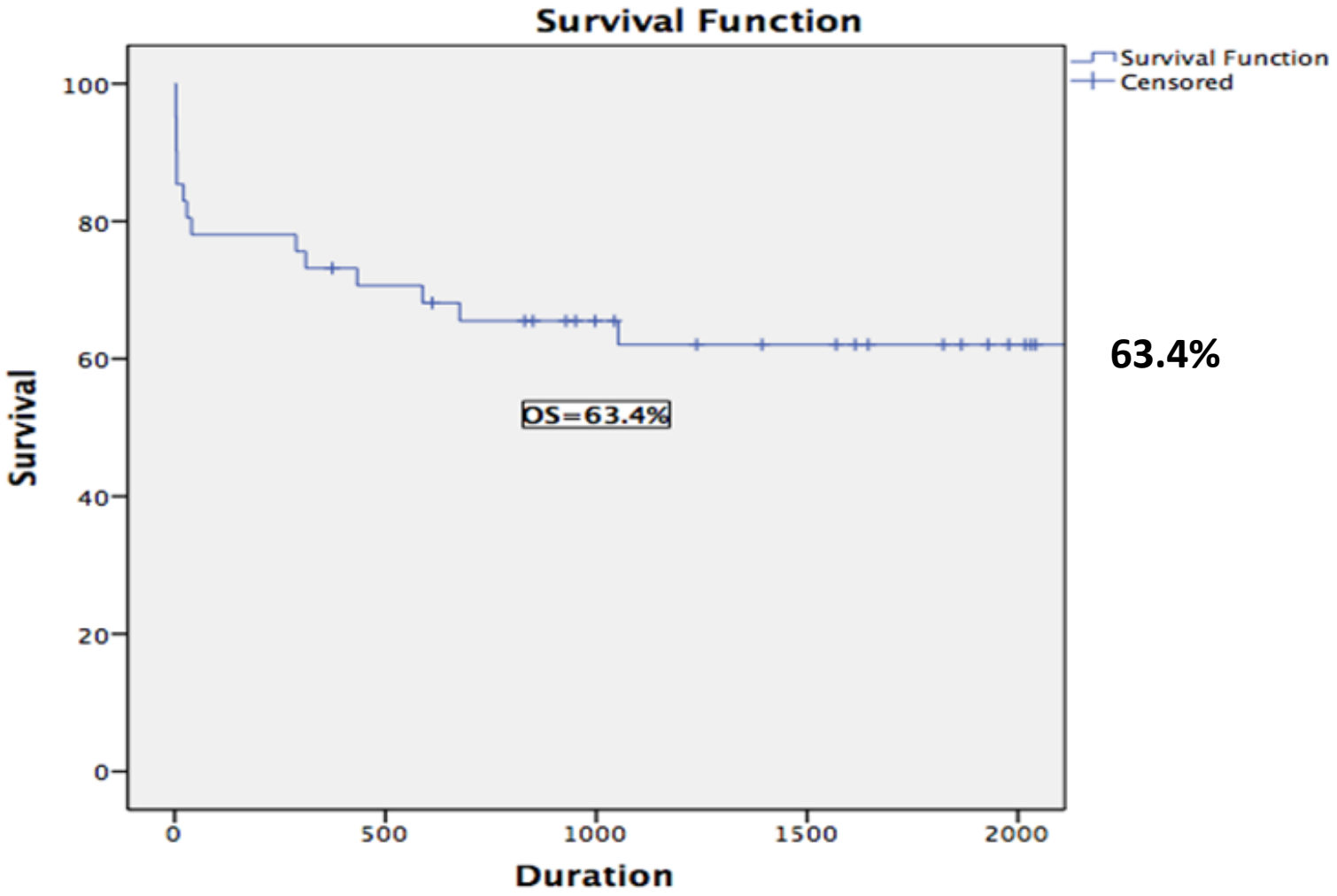
56.5%

EFS of only 41 treated Patients



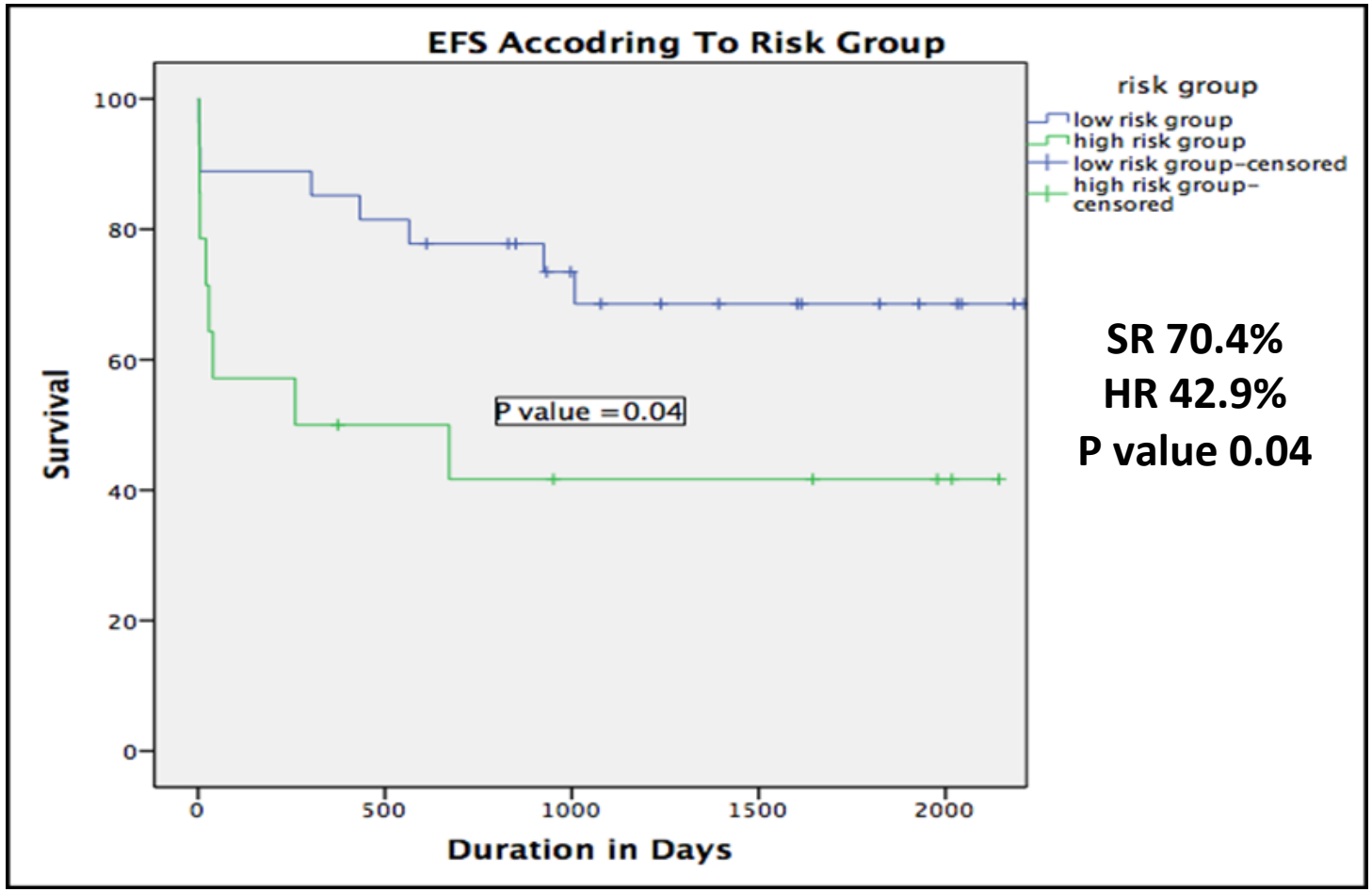
A median observation period of 31.3 months, range 2 days-80 months.

OS of only 41 treated Patients



63.4%

EFS of HR vs SR of 41 Patients

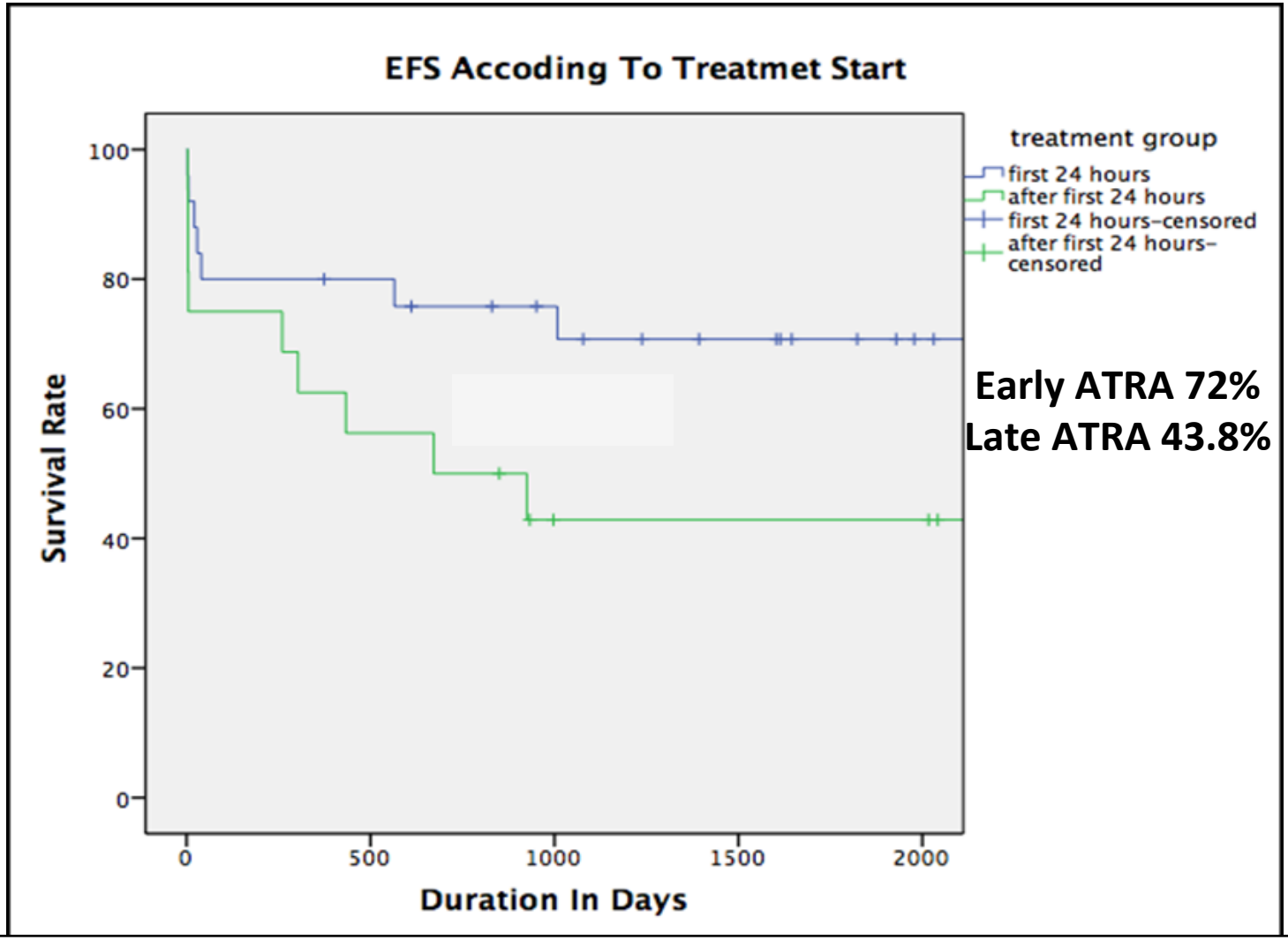


SR 70.4%
HR 42.9%
P value 0.04

SR 28
HR 18

EFS of 41 Patients related to Timing of ATRA administration

Early ATRA 25
Late ATRA 16



Early ATRA 72%
Late ATRA 43.8%

Limitations

- Supportive care
- ATRA not supplied by MoH for the last 2 years
- ATO not available
- Difficulties in confirming APL diagnosis and assessing the coagulation profile

Conclusions

- These results are of particular relevance as this subgroup of AML seems to have a high prevalence in Iraq
- It clearly demonstrates that modern therapeutic strategies, adapted to the local reality, can be effectively implemented through international collaborative efforts even in countries with limited resources.

Acknowledgement

- **Our patients and staff**
- **Rome University: Franco Mandelli, Anna Maria Testi, Maria Lusia Moleti, Francesca Mancini.**
- **GIMEMA: Alfonso Piciocchi**
- **NGOs: (INTERSOS, JIMNET)**

Thank you


If you tell the truth, you don’t have to remember any thing
2017/09/18 13:31

Protocol design

Phases of therapy	Drugs
INDUCTION	ATRA ± DNR (all patients)
CONSOLIDATION	Risk-adapted
MAINTENANCE	ATRA + MTX + 6-MP (all patients)

Risk Groups

Low risk:	**WBCc < 10 x 10^9/L , not requiring the addition of anthracyclines during ATRA induction**
High risk:	**WBCc ≥ 10 x 10^9/L, or WBC < 10 x 10^9/L requiring the addition of anthracyclines during ATRA induction**

Impact of international collaboration on the prognosis of childhood acute promyelocytic leukemia in Iraq

Iraqi protocol for childhood APL

Induction:
ATRA 25 mg/m²/d orally in two divided doses
(from day 1 to CR)
± daunorubicin 25 mg/m²/day i.v. infusion×2
consecutive days

Cumulative anthracycline dose
200 - 250 mg/m²

Course 3: daunorubicin 50 mg/m²/d i.v. (days 1)
± ATRA 45 mg/m²/d orally (days 1-15)

Maintenance

6-mercaptopurine 50 mg/m²/d orally
methotrexate 15 mg/m²/wk i.m or orally
ATRA 45 mg/m²/d orally from day 1 to 15/every 3 months

Anna Maria Testi
Salma Abbas Al-Hadad
Mazin Faisal Farhan Al-Jadiry
Maria Luisa Moleti
Franco Mandelli
Robin Foà

Haematologica 2006; 91:509-512

Supportive measures during induction

- Prednisone, 0.5 mg/kg/day from day 1 until the end of ATRA
- Platelet concentrates transfusions to maintain platelets > 30 x 10^9/l during the first 10 days.
- After 10 days, platelet concentrates will be transfused when platelets < 20 x 10^9/l or in presence of hemorrhages
- Packed red cell concentrates to maintain Hb levels > 7-8 g/dl
- Tranexamic acid (100 mg/kg/day), if platelets < 50 x 10^9/l., treatment has to be discontinued if platelets > 50 x 10^9/l

  (not used for the second group)
- CPP & FFP were given for those with evidence of coagulopathy

Consolidation-1° version

Low risk	High-risk
1st course: DNR 20 mg/m^2/d i.v. D1-3	**1st course:** DNR 20 mg/m^2/d i.v. D1-3 ATRA 45 mg/m^2/d x 15 days IT.MTX
2nd course: DNR 40 mg/m^2/d i.v. day 1 ARA-C 100 mg/m^2/8 hrs s.c. D1-3	**2nd course:** DNR 40 mg/m^2/d i.v. day 1 ARA-C 100 mg/m^2/8 hrs s.c. D1-3 ATRA 45 mg/m^2/d x 15 days IT.MTX
3rd course: DNR 50 mg/m^2/d i.v. day 1	**3rd course:** DNR 50 mg/m^2/d i.v. day 1 ATRA 45 mg/m^2/d x 15 days IT.MTX

Treatment Schedule
Induction-October 2009

All patients	
Low risk	**High risk**
ATRA 25 mg/m^2/day x 30 ds +DNR 25 mg/m^2 EOD for 4 doses	ATRA 25 mg/m^2/day x 30 ds +DNR 25 mg/m^2 EOD for 4 doses starting from day 1

Treatment Schedule
Consolidation October 2009

Low risk	High-risk
1st course: DNR 20 mg/m^2/d i.v. D1-3 ATRA 45 mg/m^2/d x 15 days	**1st course:** DNR 20 mg/m^2/d i.v. D1-3 ATRA 45 mg/m^2/d x 15 days IT.MTX
2nd course: DNR 40 mg/m^2/d i.v. day 1 ARA-C 100 mg/m^2/8 hrs s.c. D1-3 ATRA 45 mg/m^2/d x 15 days	**2nd course:** DNR 40 mg/m^2/d i.v. day 1 ARA-C 100 mg/m^2/8 hrs s.c. D1-5 6-TG 70 mg/m^2/24 h orally D1-5 ATRA 45 mg/m^2/d x 15 days IT.MTX
3rd course: DNR 50 mg/m^2/d i.v. day 1 ATRA 45 mg/m^2/d x 15 days	**3rd course:** Mtz 10mg/m^2/d i.v. D1-3 VP-16 100 mg/m^2/d i.v. D1-3 ATRA 45 mg/m^2/d x 15 days IT.MTX

Treatment Schedule
Maintenance

6-MP 50 mg/m^2/d P.O.
MTX 15 mg/m^2/w P.O.
ATRA 45* mg/m^2/d x 15 days every 12 weeks
Total duration: 2 years
Cumulative anthracycline dose: 150-350 mg/m^2

* 25 mg/m^2/d from January 2008

APL Iraqi Protocol

	First version		Amended version	
	Sept. 2003-Sept. 2009		Oct. 2009- June 2013	
Induction	ATRA 25 mg/m^2/day x 30 days ± DNR 25 mg/m^2		ATRA 25 mg/m^2/day x 30 days +DNR	
	SR	**HR**	**SR**	**HR**
Consolidation 1	DNR	DNR+ATRA	DNR +**ATRA**	DNR+ATRA
Consolidation 2	DNR+LD-CA	DNR+LD-CA+ATRA	DNR+LD-CA+**ATRA**	DNR+LD-CA+**6-TG**+ATRA
Consolidation 3	DNR	DNR+ATRA	DNR+**ATRA**	**MTZ+VP16**+ATRA
Maintenance	ATRA + MTX + 6MP		ATRA + MTX + 6MP	
Cumulative ATRA dose	3000 mg/m^2	4125 mg/m^2	**4125 mg/m^2**	4125 mg/m^2
Cumulative anthracycline dose	150 mg/m^2	250 mg/m^2	200 mg/m^2	320 mg/m^2
Cumulative cytarabine dose	900 mg/m^2	900 mg/m^2	900 mg/m^2	900 mg/m^2