Prolonged ATO and ATRA therapy for relapsed acute promyelocytic leukemia

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7th INTERNATIONAL SYMPOSIUM ON ACUTE PROMYELOCYTIC LEUKEMIA

Rome, 24-27 September 2017

Background

- ATO-ATRA is the standard salvage regimen for relapsed APL

- Optimal consolidation strategy remains controversial (auto-SCT vs allo-SCT vs other therapies)

Age, mCR1 duration, PCR status after salvage, age/fitness for SCT

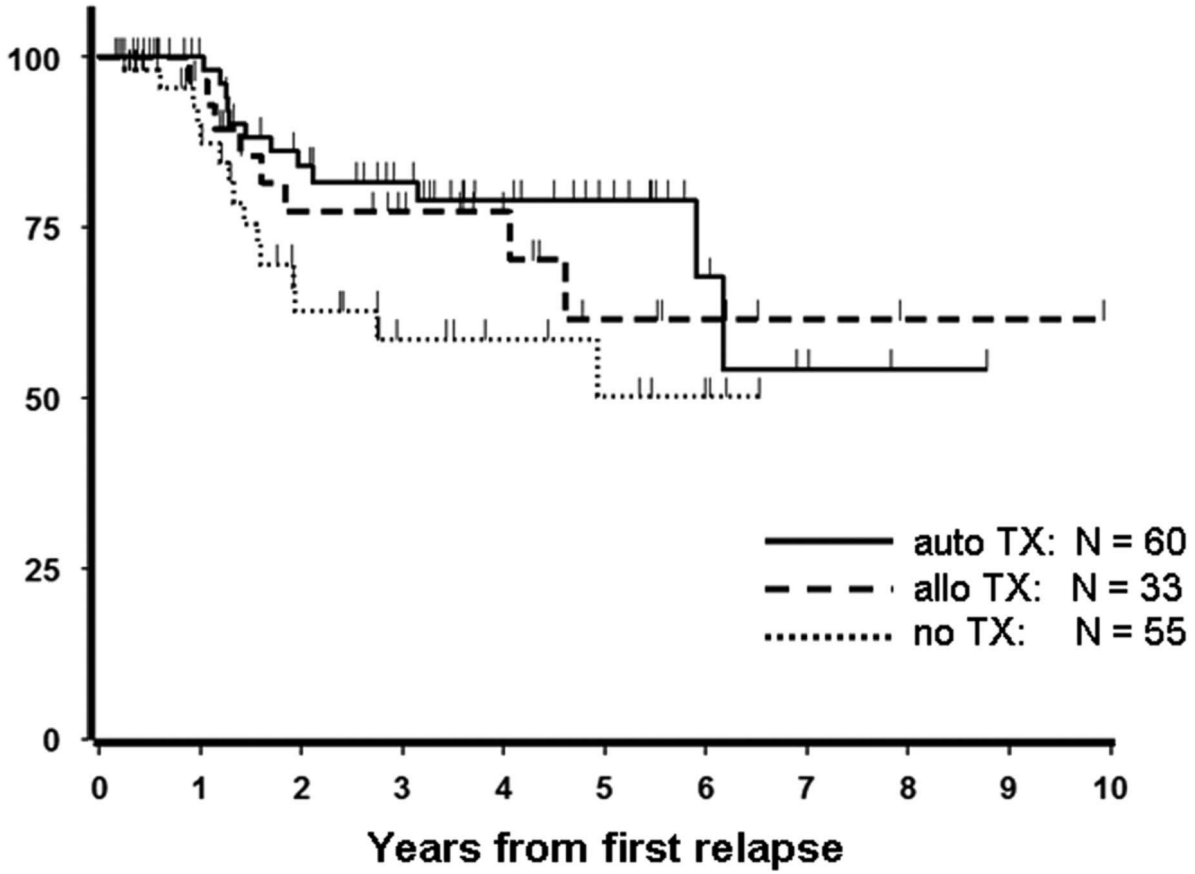
Auto vs Allo vs non-HSCT

Reference	Type	Arms	Pts (n)	EFS	OS
Yanada et al, 2013	Phase II	ATO+ auto	35	65	77
Fujita et al, 2013	Retro	Auto	6	41	83
		Allo	21	71	76
		Non-HSCT	30	45	75
Pemmaraju et al, 2013	Retro	Auto	10	78	85
		Allo	17	40	49
		Chemo	16	-	40
Ramadan et al, 2012	Retro	Allo	31	-	62
Thirugnanam et al, 2009	Retro	Auto	14	83	100
		Non-HSCT	19	34	38
Chakrabarty et al, 2014	Retro	Auto	62	63	75
		Allo	232	50	54
Lengfelder et al, 2015	Registry	Auto/Allo	33/60	-	80
		Non-HSCT	55	-	59

Auto-SCT vs Allo-SCT vs other therapies

ELN European LeukemiaNet

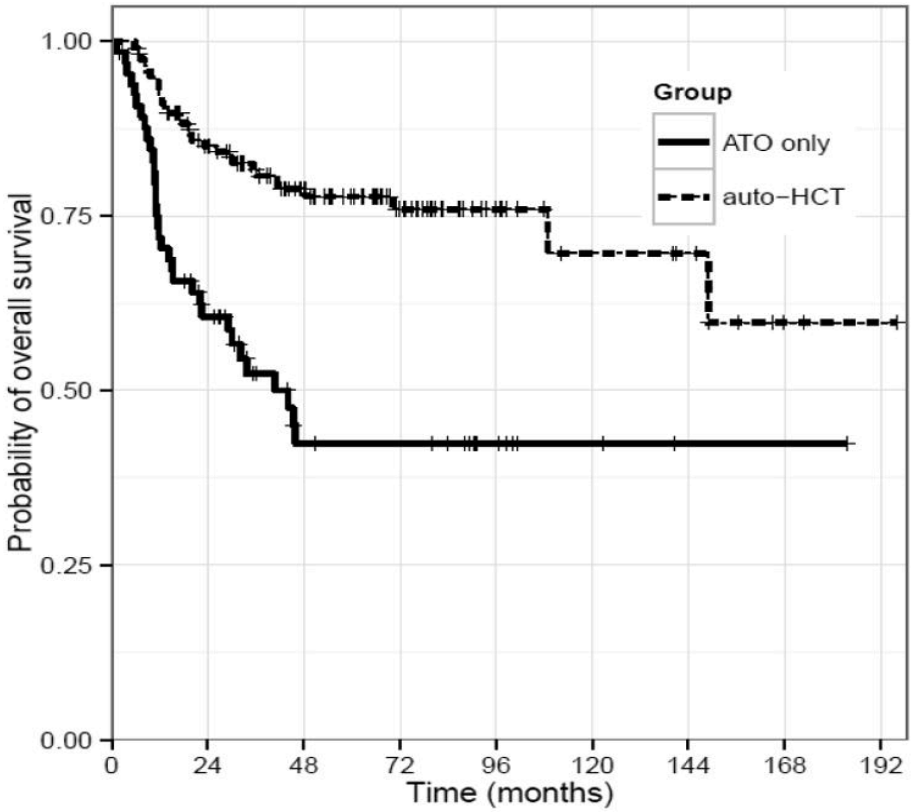
PROMYSE
A pan-European registry for relapsed Acute Promyelocytic Leukemia patients



Lengfelder et al, Leukemia 2015

Auto-SCT vs ATO alone

242 APL in CR2 (CIBMTR, India, Iran, EBMT)



Variable	HR	95% Lower	95% Upper	p-value
Auto-HCT (Y vs N)	0.495	0.345	0.710	< 0.001
CR1 time (continuous)	0. 978	0.965	0.991	< 0.001

- 67 ATO-only (76% received ATO front-line)
- 120 auto-SCT (16% received ATO front-line and 59% for salvage)

Ganzel et al, Bone Marrow Transplantation 2016

Prolonged therapy with ATO+ATRA

Efficacy of prolonged therapy with combined arsenic trioxide and ATRA for relapse of acute promyelocytic leukemia

by Massimo Breccia, Laura Cicconi, Clara Minotti, Roberto Latagliata, Laura Giannì, and Francesco Lo-Coco

Haematologica 2011 [Epub ahead of print]

UPN	Sex/age*	Relapse risk	Previous treatments	Duration of previous CR(s)	Disease status at time of ATO+ATRA Initiation	Outcome
1	M/51	Low	AIDA§	15 months	1st molecular relapse	relapsed at 10 mos
2	M/54	Interm	AIDA	12 months	1st molecular relapse	CRm^ (22+ mos)
3	F/46	Interm	AIDA	32 months	1st molecular relapse	CRm (28+ mos)
4	F/70	Interm	AIDA	28 months	1st molecular relapse	CRm (18+ mos)
5	M/38	Interm	AIDA	84 months	1st EM° and molecular relapse	CRm (39+ mos)
6	F/32	Interm	AIDA	48 months	1st molecular relapse	CRm (50+ mos)
7	M/61	interm	AIDA	17 months	1st molecular relapse	CRm (14+ mos)
8	M/69	Low∞	AIDA / GO# + ATRA	22 months /12 months	2nd hematologic relapse	CRm (31+ mos)
9	M/52	High	AIDA / ARA-C + MTZ@	17 months /13 months	2nd molecular relapse	CRm(11+ mos)

Aims

- Verify in a larger cohort of relapsed APL patients the efficacy of a prolonged ATO-ATRA therapy not followed by auto/allo SCT

Patients and methods

- 22 adult patients with relapsed APL treated between 2006-2017 in 2 Italian Institutions (Policlinico Tor Vergata and Policlinico Umberto I, Rome) after obtaining IRB approval

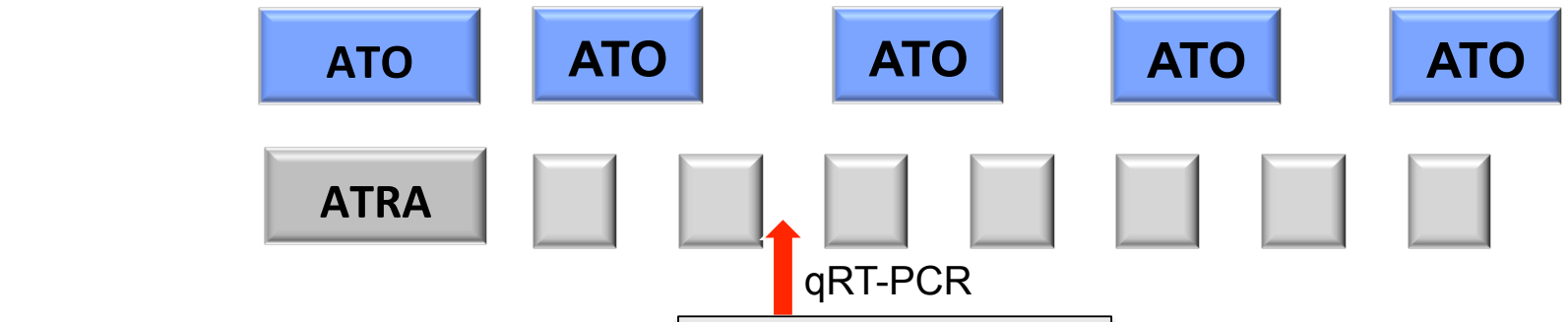
- All patients received ATO-ATRA (Lo-Coco, NEJM 2013) for induction and consolidation followed or not by transplant procedures.

- Molecular analysis of PML/RARA was carried out by RQ-PCR (according to standardized methods)

Patient characteristics

Age, median (range)		43.5 (18-80)
Duration of previous CR, median (range)		32.5 (5-120)
Relapse	1 st relapse	18
	> 1 st relapse	4
Type of relapse	Hematological	7
	Molecular	14
	Extramedullary	3
Front-line therapy	AIDA	20
	AIDA “elderly”	2

Patient outcome (I)



CRm: 20/22 (90%)

Transplant: 2 pts

Autologous: 1

Allogeneic (HLA-id): 1

No transplant: 18 pts

ATO-ATRA: median 5 cycles (2-5)

-Long previous CRm: 9

-Elderly/unfit: 5

-Refusal of HSCT: 2

-Lack of donor: 2

Patient outcome (II)

Median follow-up: 58 months (21-128)

UPN	HSCT	PCR after therapy	Outcome
1	No	Negative	CRm, 20+
2	No	Negative	CRm, 60+
3	No	Negative	CRm, 62+
4	Auto-HSCT	Negative	CRm, 105+
5	No	Negative	CRm, 60+
6	No	Negative	CRm, 38+
7	No	Negative	CRm, 120+
8	No	Negative	CRm, 128+
9	No	Negative	CRm, 62+
10	No	Negative	CRm, 50+
11	No	Negative	CRm, 110+
12	No	Negative	CRm, 109+
13	No	Negative	CRm, 72+
14	No	Negative	CRm, 66+
15	No	Negative	Death in CRm
16	Allo-HSCT	Negative	Relapsed
17	No	Negative	Relapsed
18	No	Negative	Relapsed
19	No	Negative	Relapsed
20	No	Negative	Relapsed
21	No	Positive	Resistant
22	No	Positive	Resistant

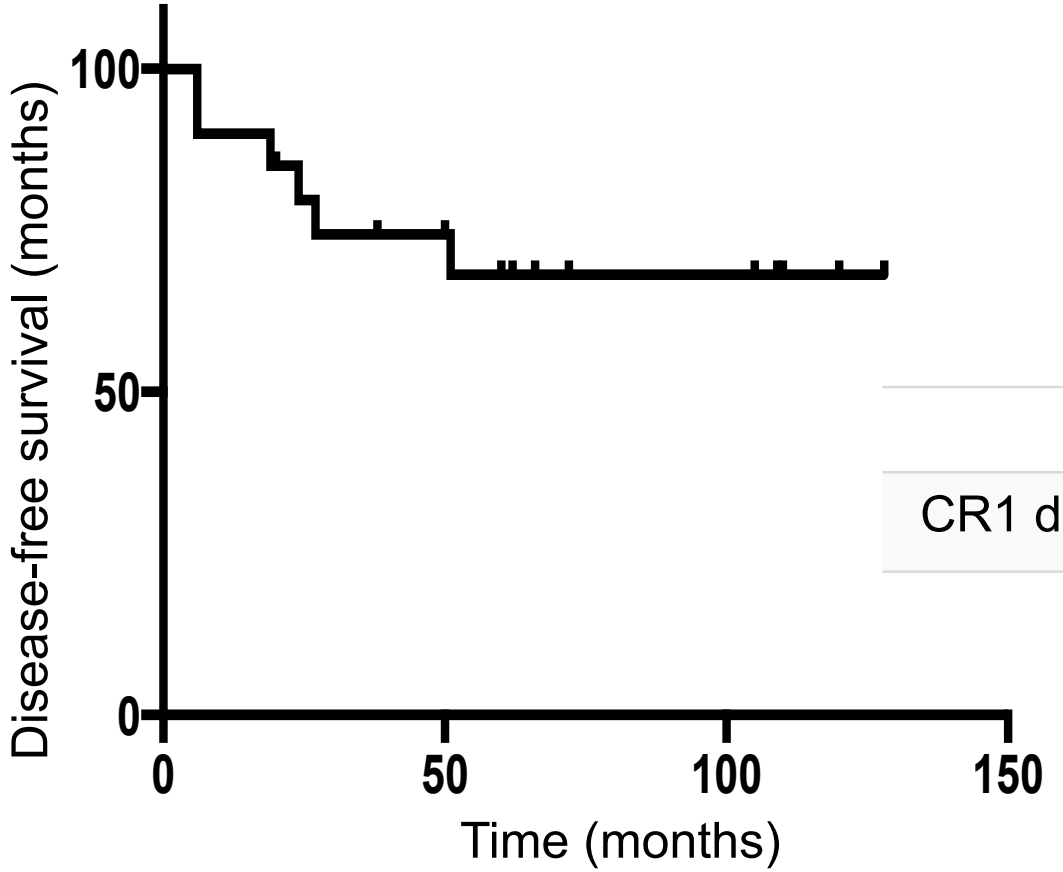
14 alive in CRm (68%)

1 death in CRm

7 rel/refractory (32%)

Survival analysis

Median follow-up: 58 months (21-128)



Variable	CI 95%	P-value
CR1 duration, months	0.19-0.8	0.0056

Conclusions

- Our data suggest that prolonged ATO-ATRA therapy without SCT intensification might be an option for relapsed APL
- Long CR1 is associated with a higher probability of long-term CRm with prolonged ATRA-ATO
- Prospective studies are warranted to confirm our preliminary data

Acknowledgements

UNIVERSITA' degli STUDI di ROMA TOR VERGATA

M. Divona
C. Ciardi
A. Ferrantini
S. Lavorgna
T. Ottone
V. Alfonso
L. Iaccarino
G. Falconi
E. Fabiani

Francesco Lo-Coco
Maria Teresa Voso
William Arcese

Adriano Venditti
Sergio Amadori
Luca Franceschini
Manuela Rizzo

AIRC

ASSOCIAZIONE ITALIANA
CONTRO LE LEUCEMIE-LINFOMI E MIELOMA
ONLUS

SAPIENZA
UNIVERSITÀ DI ROMA

Massimo Breccia
Robin Foà
R. Latagliata
M. Molica