Outcome of relapsed/refractory acute promyelocytic leukaemia in children, adolescents and young adult patients — a 25-year Italian experience

Acute promyelocytic leukaemia (APL) is a rare subtype of childhood acute myeloid leukaemia (AML), accounting for 5–12% of all AML cases. Treatment with all-*trans*-retinoic acid (ATRA) and anthracyclines yields complete remission (CR) rates >90% and 10-year event-free survival (EFS) rates around 80%.[1–3] The recent front-line arsenic trioxide (ATO)-based regimens have further improved the APL outcome by reducing toxicity and preventing relapse.[4–6] Relapsed APL patients are a rare and heterogeneous group, whose prognosis depends on front-line treatment and time elapsing between diagnosis and recurrence. Currently, ATO is the treatment of choice for relapsed APL. Due to the rarity of relapsed childhood APL, 17–27% in ATRA- and chemotherapy-[1,3,7–9] and 4% in ATO-containing regimens,[10] it will be difficult, in the future, to design future prospective comparative trials for these patients. In an attempt to design therapeutic guidelines, recommendations on management of relapsed/refractory paediatric APL have been published recently.[11]

Here, we report the Italian experience on 51 patients <18 years at diagnosis, treated between May 1994 and May 2017 in 22 AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) centres, who experienced relapsed or refractory disease. All patients received front-line ATRA and chemotherapy (CT), according to the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto)/AIEOP AIDA-0493, -2000 and ICC-APL01 protocols.[1,2] All were registered at the GIMEMA database.

Salvage strategies were heterogeneous according to the time of the events and ATO availability at the various centres. Until January 2008, salvage regimens were based on ATRA and intensive chemotherapy; options for consolidation were either autologous or allogeneic haematopoietic stem cell transplantation (HSCT) or different maintenance approaches for patients not eligible for HSCT.

After January 2008, re-induction consisted of ATO until CR, followed by ATRA and a second ATO cycle. Patients in molecular CR continued with ATO + gentuzumab ozogamycin (GO); those who had a positive molecular residual disease received GO followed by autologous or allogeneic HSCT. Details of salvage treatments are given in the Supporting Information.

Informed consent was obtained from all parents and/or patients. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration of 1975.

At the time of the event (relapse/refractoriness), patients were risk-stratified according to the new APL relapse risk classification[11] as: standard risk, those with late and very late relapse, or extramedullary relapse promptly responding to salvage treatment; high risk, those with early relapse, or refractory to first-line therapy; and those relapsed at any time, with late response to salvage therapy.

Details of definitions and statistical analysis are given in the Supporting Information.

At diagnosis, 26 (51%) patients were classified as standard risk [white blood cells (WBC) $<10 \times 10^9$/l] and 25 (49%) as high risk (WBC $\geq 10 \times 10^9$/l); 25 patients (49%) had received AIDA-0493, 12 (24%) AIDA-2000 and 14 (27%) ICC-APL-01, as first-line therapy. Median age at refractoriness/relapse was 13·9 years (range, 2·4–24·9); 43 (84%) relapsed (21 haematologic; 16 molecular; one isolated extramedullary; five extramedullary+molecular) and eight (16%) were refractory. Based on the time to relapse, the 43 who relapsed were classified as: 14 early, 15 late and 14 very late. At the time of the study, according to the new relapse risk classification, 22 (43%) patients were standard risk and 29 (57%) high risk. Thirty-three (65%) patients received ATRA + CT salvage therapy and 18, ATO + ATRA. The distribution of patients according to the salvage regimen, disease status and biological characteristics is described in Table I.

Two out of the 33 ATRA + CT patients died during induction; 31 achieved a molecular CR; 18 were consolidated with either autologous (seven patients) or allogeneic (11 patients) HSCT (four relapses; one death; 13 alive in CR2). Thirteen patients continued different maintenance regimens (eight alive in CR2; five relapses). The 10-year overall survival (OS) and EFS are 72·1% [95% confidence interval (CI): 58·2–89·4] and 62·9% (95% CI: 48·2–82·0) respectively.

None of the 18 patients re-induced with ATO developed induction fatal complications. All achieved a molecular CR; seven were consolidated with an autologous (one patient) or an allogeneic (six patients) HSCT (two relapses; five alive in CR2); 11 patients continued ATO (two haematologic relapse; nine alive in CR2). The 10-year OS and EFS are 94·4% (95% CI: 84·4–100) and 77·8% (95% CI: 60·8–99·6), respectively.

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Table I. Clinical and biologic characteristics and distribution of patients according to salvage treatment.

Characteristics	*n*	Overall *n* = 51	ATRA + CT *n* = 33	ATO *n* = 18	*P* value
Gender: M/F	51	29 (57%)	20 (61%)	9 (50%)	0·56
		22 (43%)	13 (39%)	9 (50%)	
Age – yrs at time of event; median (range)	51	13.9 (2.4–24.9)	13.9 (2.9–22.3)	13.5 (2.4–24.9)	0·75
Morphology:	50				<0·001
M3c		39 (78%)	30 (91%)	9 (53%)	
M3v		11 (22%)	3 (9·1%)	8 (47%)	
Not available		1	0	1	
PML breakpoint	48				0·89
bcr1		23 (48%)	14 (45%)	9 (53%)	
bcr2		3 (6·2%)	2 (6·5%)	1 (5·9%)	
bcr3		22 (46%)	15 (48%)	7 (41%)	
Not available		3	2	1	
First-line therapy	51				<0·001
AIDA-0493		25 (49%)	24 (73%)	1 (5·6%)	
AIDA-2000		12 (24%)	9 (27%)	3 (17%)	
ICC-APL-01		14 (27%)	0	14 (78%)	
First event	51				0·43
Relapse		43 (84%)	29 (88%)	14 (78%)	
Refractory disease		8 (16%)	4 (12%)	4 (22%)	
Type of relapse	43				0·004
Haematologic		21 (49%)	19 (66%)	2 (14%)	
Molecular		16 (37%)	7 (24%)	9 (64%)	
Extramedullary		1 (2·3%)	0	1 (7·1%)	
Extram.+molecular		5 (12%)	3 (10%)	2 (14%)	
Time to relapse	51				0·81
Early		14 (27%)	9 (27%)	5 (28%)	
Late		15 (29%)	10 (30%)	5 (28%)	
Very late		14 (27%)	10 (30%)	4 (22%)	
Refractory		8 (16%)	4 (12%)	4 (22%)	
Risk category at R/R	51				>0·99
SR		22 (43%)	14 (42%)	8 (44%)	
HR		29 (57%)	19 (58%)	10 (56%)	

ATRA, all-trans-retinoic acid; ATO, arsenic trioxide; PML, promyelocytic leukaemia; R/R, relapsed/refractory; SR, standard-risk; HR, high-risk.

Details regarding outcome, consolidation for patients with haematologic, molecular or extramedullary relapse or with refractory disease are described in Tables SI–SIV.

Molecular CR rate in the whole group of 51 patients was 96%; CR rate was identical in patients with haematologic (95%) and molecular relapse (95%); all eight refractory patients achieved a molecular CR (four ATRA + CT and four ATO).

Among the 49 patients in CR2, 25 (51%) received HSCT (autologous, eight; allogeneic, 17) as consolidation therapy; the molecular status at transplant time was available in 18/25 patients and all were negative. There was no significant difference in the proportion of transplanted and non-transplanted patients between haematologic (50% HSCT vs. 50% CT) and molecular relapse (45% HSCT vs. 55% CT), type of re-induction therapy (no ATO-HSCT, 58% vs. ATO-HSCT, 39%) and risk category at relapse/refractoriness (standard risk, 45% vs. high risk, 55%).

With a median follow-up of 176·26 months from the time of relapse/refractoriness (range 0·7–314), the 10-year OS and EFS are 79·4% (95% CI 68·7–91·7) and 67·7% (95% CI 55·8–82·2; Fig 1A,B).

Patients treated in molecular *versus* haematologic relapse, had a more favourable outcome: 10-year OS 87·5% vs. 65·9%, $P = 0·135$ [hazard ratio (HR) 0·32 95% CI 0·07–1·55]; EFS 75% vs. 56·7%, $P = 0·328$; (HR 0·56 95% CI 0·17–1·82). Time to relapse had no prognostic influence on OS ($P = 0·234$) and EFS ($P = 0·214$); however, patients in very late and late relapse had a better OS (84·4% and 80·0%; very late vs. early: HR 0·34, 95% CI 0·07–1·74; late vs. early HR 0·51 95% CI 0·12–2·13) and EFS (84·4% and 66·7%), compared to those with an early relapse (OS 63·5%; EFS 50%; very late vs. early: HR 0·21 95% CI 0·04–1·03; late *versus* early HR 0·61 95% CI 0·19–1·93; Fig S1). The 10-year OS and EFS were significantly better for standard-risk, compared to high-risk patients: OS 95·5% vs. 66·5%, $P = 0·017$

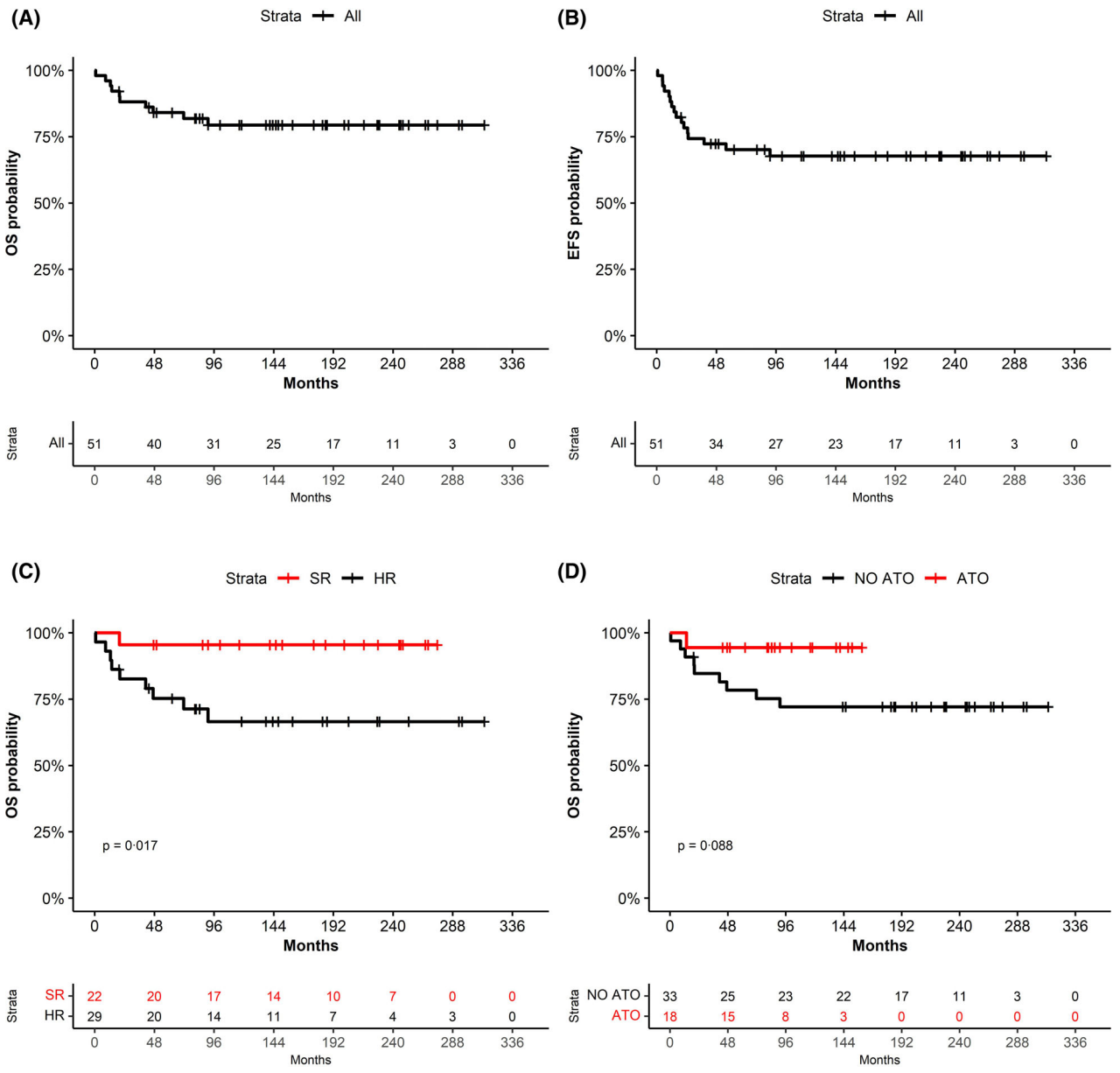

Fig 1. Ten-year overall survival (OS; A) and event-free survival (EFS; B) of refractory/relapsed paediatric acute promyelocytic leukaemia patients. Ten-year overall survival (C) of patients classified as standard and high-risk and 10-year overall survival (D) of patients classified by type of re-induction therapy.

(HR 0·12 95% CI 0·02–0·97); EFS 95·5% vs. 46·0%, $P < 0·001$ (HR 0·06 95% CI 0·01–0·48; Fig 1C).

No significant difference in OS and EFS was observed between patients treated with ATRA + CT and those with ATO (OS 72·1% vs. 94·4%, $P = 0·087$; HR 0·20 95% CI 0·03–1·56; EFS 62·9% vs. 77·8%, $P = 0·390$; HR 0·61 95% CI 0·20–1·90; Fig 1D). However, the ATO regimen was associated with a trend towards a better OS in high-risk patients (OS 90% vs. 56·1%, $P = 0·119$). Cumulative incidence of relapse (CIR) was 25·9% with no differences between the ATRA + CT and ATO group (CIR 27·8% vs. 22·2%; $P = 0·763$).

Finally, univariate analysis for OS and EFS showed no significant differences between transplanted and non-transplanted patients (OS: HR 2·43; 95% CI: 0·60–9·82, $P = 0·213$; EFS HR 1·10, 95% CI 0·38–3·17, $P = 0·855$), and between those consolidated with an autologous or allogeneic HSCT (OS 87·5% vs. 76·0% and EFS 72·9% vs. 70·6%).

Although our study is based on a retrospective small series of patients managed over 25 years, it does suggest a potentially curative effect of different salvage regimens for relapsed/refractory paediatric APL (molecular CR 96%; 10-year OS and EFS: 79·4% and 67·7% respectively).

The optimal post-remission therapy for paediatric patients in CR2 after salvage with either ATO, or ATRA + CT, remains undefined. In the largest paediatric series, no significant differences in EFS and OS have been observed between autologous and allogeneic HSCT.[12] The molecular disease status at transplant has emerged as an important prognostic variable.[13-16] The retrospective analysis from the European Acute Promyelocytic Leukemia Group comparing autologous and allogeneic HSCT in relapsed adult APL demonstrated the efficacy of autologous HSCT performed in molecular CR.[17] In the recent analysis of relapsed APL treated upfront with ATO and salvaged with ATO-based regimens, an autologous HSCT was offered in second molecular CR; the 5 year OS and EFS were 90·3% and 87·1% respectively.[17]

In our series, 25 patients received a HSCT; no statistical differences in OS and EFS were observed between auto- and allo-transplanted patients; in addition, the univariate analysis for OS and EFS did not show a difference between transplanted and non-transplanted patients.

Several studies have identified different prognostic factors in relapsed APL. A first CR duration <12–18 months has been associated with a higher treatment failure.[16,18] In our series, time between diagnosis and relapse had no significant prognostic influence on OS and EFS; however, few patients in very late or late relapse had a better OS and EFS compared to those with an early relapse. The 10-year OS and EFS were significantly better for standard-risk compared to high-risk patients ($P = 0{\cdot}017$; $P < 0{\cdot}001$). In addition, although not statistically significant, the OS of high-risk patients treated with the ATO regimen was better than that of patients re-induced with ATRA + CT.

In summary, in our retrospective study both salvage regimens (ATRA + CT and ATO) were effective in inducing a molecular CR for relapsed/refractory paediatric APL; less early toxicity was observed with ATO treatment compared to ATRA + CT. The new risk stratification of paediatric relapsed APL allowed us to identify patients with lower or higher risk of treatment failure with salvage therapy.

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Author contributions

AMT contributed to the design of the studies, enrolled patients, analyzed data and wrote the manuscript; SM analyzed data and wrote the manuscript; DD performed diagnostic studies and MRD evaluation; AP collected, interpreted, and analyzed the data and performed the statistical analysis; GM, CR, FT, CM, LLN, NS, RM, MVM, OZ, DO, SL, CP, PP and MZ enrolled patients, collected clinical data and contributed in editing and reviewing the manuscript; VA analyzed the data; RF and FL contributed to the design of the studies, edited, and critically revised the paper and approved the final version. All authors provided critical feedback, edited and approved the typescript.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Induction results.

Table SII. Patients reinduced with ATRA + chemotherapy or ATO: outcome by type of consolidation.

Table SIII. Patients re-induced with ATRA + chemotherapy: type of consolidation and outcome.

Table SIV. Patients re-induced with ATO/ATRA: type of consolidation and outcome.

Fig S1. Ten-year overall survival (A) and event-free survival (B) by time to relapse.

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