



**Review Article**

## Has Hematopoietic Stem Cell Transplantation a Role in the Treatment of Children and Adolescents with Acute Promyelocytic Leukemia?

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract.** The past three decades have brought major therapeutic advances in treating acute promyelocytic leukemia (APL) both in adults and children. The current state-of-the-art treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) in combination or not with chemotherapy results in long-lasting remission and cure in more than 90% of newly diagnosed patients. These treatments have made relapse a rare event. The detection of PML-RARA transcript by polymerase chain reaction (PCR) during treatment and follow-up can predict a hematological relapse. All studies have suggested a survival benefit in patients with molecular relapse given pre-emptive therapy compared with those treated at the time of overt hematological relapse. ATO-based regimens seem to be effective for achieving a second molecular complete remission (CR). Patients in second molecular CR are generally considered candidates for autologous hematopoietic stem cell transplant (HSCT), while for those with a persistent molecular disease, allogeneic HSCT should be offered if a suitable donor is identified.

Except for sporadic pediatric reports, most of the evidence for using HSCT to treat relapsed/refractory APL comes from adult literature. Therefore, we now provide a review of published pediatric data that evaluated the role of HSCT in children with refractory/recurrent APL disease.

**Keywords:** Acute promyelocytic leukemia; Relapse; Hematopoietic stem cell transplant; Children; Adolescents.

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**Introduction.** The new treatment approaches for pediatric patients with newly diagnosed acute promyelocytic leukemia (APL), combining a differentiation agent, all-trans retinoic acid (ATRA) and anthracyclines, result in a complete remission rate of 96-97 %, and a virtual absence of primary resistance.<sup>1-6</sup> These cure rates are currently obtained with risk-adapted treatments where the intensity and duration of induction and consolidation therapy are modulated according to clinical and biological parameters at disease presentation and early molecular response to treatment. The 5-year overall survival (OS) and event-free survival (EFS) for

children treated with Italian AIDA 2000 and International ICC-APL-01 protocols, both risk-adapted strategies combining ATRA and chemotherapy, are 94%-95% and 80-85%, respectively.<sup>1,2</sup> These protocols enrolled a high number of children and adolescents (127 and 258, respectively); better results are reported for patients defined at standard risk (SR, WBC<10x10<sup>9</sup>/L) with an OS rate of 98% compared to 89% achieved in patients at high-risk (HR, WBC≥10x10<sup>9</sup>/L).

More recently, the ATRA+ATO combination, chemo-free approach, associated or not to chemotherapy for HR children, further decreased the relapse rate in

these patients. Results are still limited to a small number of young patients, but more than 95% of these patients are alive and leukemia-free at two years.<sup>7-10</sup>

Minimal residual disease (MRD) monitoring based on detection of PML-RARA transcript, employing first, qualitative and then quantitative polymerase-chain-reaction (PCR; RT-and RQ-PCR) technologies after the second or third consolidation course and during patients' follow-up, gave the opportunity to show an early detection of molecular relapse in the bone marrow, before the occurrence of hematologic relapse.<sup>2,11,12</sup> Patients in molecular relapse, especially with ATO-based regimens, have a higher probability of achieving a second molecular complete remission (CR), with no risk of exacerbation of leukemic promyelocytes-related coagulopathy compared with patients with overt haematologic relapse.<sup>13</sup>

### **Hematopoietic Stem Cell Transplantation as Part of APL Salvage Therapy (Allogeneic and Autologous).**

In this context, hematopoietic stem cell transplant (HSCT) is no longer indicated in the first-line treatment, but it may play a crucial role in consolidating remission in patients in second CR or beyond after salvage therapy relapsed APL.<sup>14-16</sup> For patients in second CR, consolidation with HSCT, either autologous (auto) or allogeneic (allo) resulted in better survival outcomes than non-transplant strategies. Although HSCT is generally accepted therapy for APL in second CR, the choice of allo- versus auto-HSCT remains controversial. It is uncertain whether the increased treatment-related mortality (TRM) generally associated with allo-HSCT is compensated for by a lower relapse rate due to the graft versus APL effect.<sup>15,17</sup> It has also been suggested that auto-HSCT's outcome is improved if molecularly negative cells are collected. The recent analysis of the Acute Leukemia Working Party (ALWP) of the European Blood Bone Marrow Transplantation (EBMT) included 341 and 228 APL patients in second CR who underwent auto-HSCT and allo-HSCT, respectively.<sup>16,17</sup> The EFS was significantly higher in the auto-group (75%) compared to the allo-group (55%); auto-HSCT was also superior to allo-HSCT in terms of OS. In keeping with these findings, other large studies reported better OS for auto-HSCT compared to allo-HSCT.<sup>13,15-17</sup> The benefit of the graft-versus-leukemia (GVL) effect in patients undergoing allo-HSCT was widely counterbalanced by a higher TRM systematically reported in this setting compared with patients undergoing auto-HSCT. On the other hand, a second relapse after auto-HSCT is probably a clinical situation with a higher chance of subsequent salvage as compared to a second relapse after allo-HSCT. Prognostic factors associated with transplant outcomes in APL in second CR that adversely influenced overall mortality were mainly age (>40 years) and shorter first CR duration; in

addition, the molecular persistence after salvage treatment had an adverse impact on transplant outcome in multivariate analysis.<sup>16-18</sup> Regarding auto-HSCT, the previous salvage therapy with ATO was associated with delayed hematopoietic recovery after transplantation.<sup>19,20</sup> A retrospective review of 58 APL patients undergoing auto-HSCT at 21 Institutions in the United States and Japan reported that ATO exposure prior to hematopoietic stem cells collection harmed hematopoietic recovery after auto-HSCT. However, this delay does not significantly impact TRM and transplant outcome.<sup>20</sup>

Peripheral blood has been, by far, the preferred stem cell source used in most studies where auto-HSCT represented the consolidation therapy in second CR. The proportion of patients transplanted with peripheral blood in the different studies varied from 86% to 100%, including the recent EBMT study in which the proportion increased to 92%.<sup>16</sup> In contrast, the most common stem cell source in the allo-HSCT setting was bone marrow (range 64% to 87%).<sup>16</sup>

Myeloablative conditioning regimens were almost universally used for auto- and allo-HSCT, except for a few patients who received reduced-intensity regimens (RIC).<sup>21</sup> TBI-based regimens were preferred for auto-HSCT in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry data<sup>21</sup> and single-centre studies; in contrast, non-TBI-based regimens were preferred in most recent reports from EBMT registry and Japan Society of Hematology and for Hematopoietic Cell Transplantation,<sup>18</sup> as well as other single-centre studies.<sup>16</sup> Busulfan and Cyclophosphamide was the non-TBI-based regimen more frequently used.

**Pediatric Experiences.** The majority of reports on the use of HSCT for treatment of relapsed/refractory APL deal primarily with adults, making the benefit of these therapies for children unclear. Most of the published data on HSCT as a treatment for relapsed childhood APL comes from small retrospective studies. Among 31 children in the European APL93 trial (ATRA+chemotherapy), seven achieved second CR; three patients received auto-HSCT, and three underwent allo-HSCT.<sup>22</sup> One allografted patient died from graft-versus-host-disease (GVHD), while six patients remained in molecular second CR after 17 to 66 months (**Table 1**). Termuhlen et al. (2008) reported the outcome of 5 relapsed APL children who achieved a second molecular CR after reinduction therapy with ATO (4 patients) or FLAG (1 patient) and, after that, underwent auto-HSCT.<sup>23</sup> All patients remained in second molecular CR after 20 months (Table 1). Bourquin et al. (2004) reported 12 allo-HSCT performed in 11 relapsed/refractory pediatric (median age 13 years) APL patients treated between 1986 and 2003.<sup>24</sup> Most of these children were initially treated in the pre-ATRA era. All transplants were performed with a myeloablative

**Table 1.** Results of hematopoietic stem cell transplantation in pediatric APL patients in second complete remission.

Authors	N. Patients	Median Age (yrs) (range)	HSCT* period	Outcome of patients after Allo** HSCT	Outcome of patients after Auto*** HSCT
Bourquin, et al (2004)	12	11 (2-21)	1986-2003	OS° 73% TRM°° 27% RI°°° 10%	
de Botton, et al (2004)	3 3	15 (11-18)	1993-1998	1 death in CR; 2 CCR^	3 CCR
Termuhlen, et al (2008)	5	13 (3-18)	2004-2006		OS 100%; EFS^^ 100% TRM 0% RI 0%
Baidil'dina, et al (2010)	7	<18	before 2010		5 CCR; 1 on-therapy; 1 death
Dvorak, et al (2008)	21	12 (2-18)	1992-2007	OS 76%; EFS 71% TRM 19% RI 10%	OS 82%; EFS 73% TRM 0% RI 27%
	11	12 (2-18)	1992-2007		
Chakrabarty, et al (2014)	9	< 20	1995-2006		OS 75%; DFS^^^ 63% TRM 7% RI 30% OS 54%; DFS 50% TRM 31% RI 18%
	70	< 20	1995-2006		
Yamamoto et al (2020)	29	<19	1990-2014	OS 78%; DFS 75%;	OS 85%; DFS 76%
	13	<19	1990-2014		
Testi, et al (2021)	17	13.9 (2.4-24.9)	1994-2017	OS 76%; EFS 70.6% TRM 6%	OS 87.5%; EFS 72.9% TRM 0%
	8	13.9 (2.4-24.9)	1994-2017		

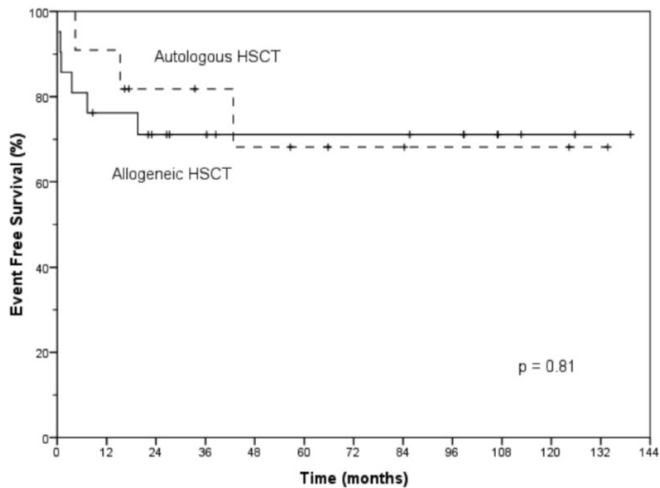
\*HSCT: Hematopoietic stem cell transplant; \*\*Allo: Allogeneic; \*\*\*Auto: Autologous; °OS: Overall survival; °°TRM: Therapy-related mortality; °°°RI: Relapse incidence; ^CCR: Continuous complete remission; ^^EFS: Event-free survival; ^^DFS: Disease-free survival.

conditioning regimen; in 7/12, a radiation-based regimen was employed. In five cases, the marrow graft was obtained from an HLA-matched relative; in the other seven children, the graft was obtained from an unrelated donor. All patients received T-cell-depleted graft. The median time for neutrophil and platelet recovery was 18.5 and 32 days. One patient relapsed 14 months after an HLA-matched related donor transplant; he received a second unrelated donor HSCT and became a long-term leukemia-free survivor. Five-year OS was 73% (median follow-up 64 months); all deaths (3 patients) were from TRM. Four of the five patients not in hematological CR at the time of transplant are disease-free survivors (**Table 1**). The potent graft-versus-leukemia effect related to allo-HSCT was evident in this set of patients.

Another pediatric study included nine patients with recurrent APL.<sup>25</sup> Salvage therapy included ATO and/or standard chemotherapy + ATRA; ATO monotherapy was used in consolidation. CD34+ cells were mobilized at molecular CR achievement, with high-dose cytarabine and granulocyte-colony-stimulating factor. One patient died before therapy; eight children achieved second molecular CR. CD34+ cell mobilization and collection were effective in seven cases. Pre auto-HSCT conditioning included melphalan in combination with high-dose cytarabine (5 patients), treosulfan (1 patient)

or busulfan (1 patient). Five patients became long-term survivors in molecular CR (follow-up 30-40 months). One patient was still on treatment, and another developed a disease recurrence and died from complications. The authors concluded that the application of ATO and auto-HSCT in relapsed pediatric APL is effective for achieving prolonged second molecular CR (**Table 1**).

Dvorak et al. (2008) reported 32 pediatric cases with relapsed/refractory APL, undergoing either auto- or allo-HSCT. According to the Eastern Cooperative Group (ECOG) E2491 Trial and the Cancer and Leukemia Group B (CALGB) C9710 trial, these children had originally received treatment from 1992 to 2005. First-line therapy had included either ATRA alone or a combination of cytarabine and anthracyclines (ECOG E2491) or ATRA associated with chemotherapy randomly followed by ATRA +anthracycline or ATO for two courses (CALGB C9710). Three children failed to achieve CR with the initial induction protocol and underwent HSCT to treat primary/resistant disease. The other 29 patients underwent HSCT after relapse, which occurred at a median of 10 months from the first CR. All these patients were in morphologic CR before transplant after various salvage regimens; 11 patients underwent auto-HSCT and 21 allo-HSCT. RT-PCR of the autograft product was negative in 6 and unknown in 5 patients. In

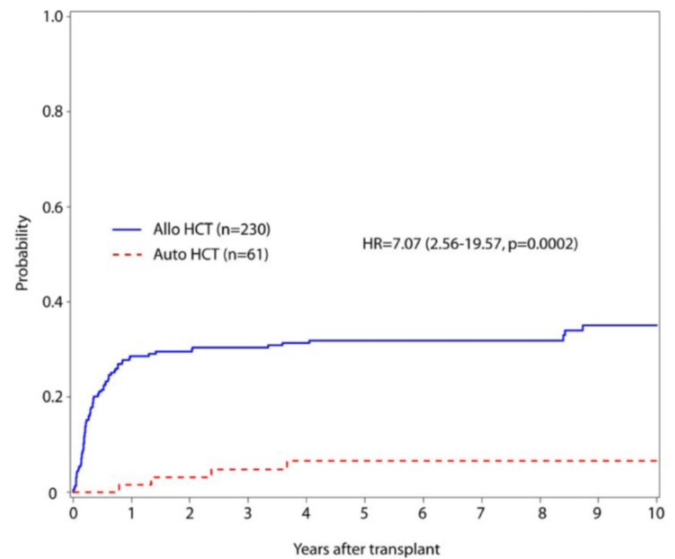


**Figure 1.** ECOG E2491 and CALGB C9710 trials. Event-free survival following hematopoietic stem cell transplant for childhood relapsed/refractory acute promyelocytic leukemia.

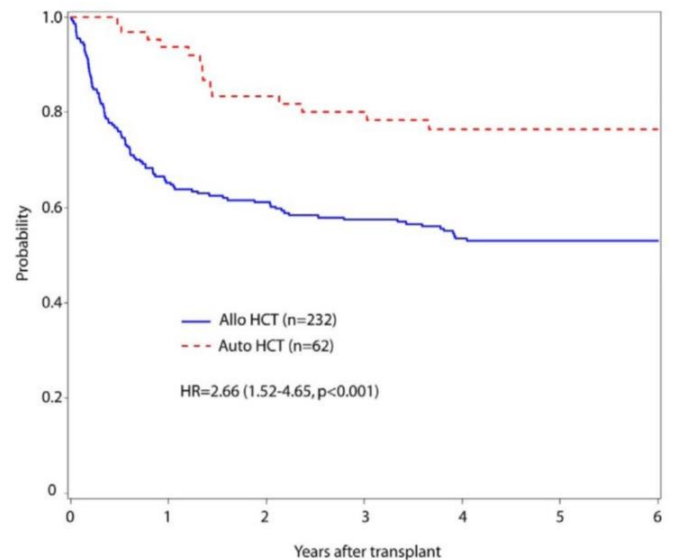
most patients, conditioning regimens consisted of cyclophosphamide combined with either total body irradiation (TBI, 13 patients) or busulfan. Other regimens added a third agent (cytarabine, etoposide or thiotepe) to this backbone. Five patients relapsed following HSCT (3 after auto-HSCT and 2 after allo-HSCT); the median time to relapse was 15.3 and 13.5 months after auto and allo-HSCT, respectively. The 5-year EFS and OS were 82% and 76% after auto-HSCT and 73% and 71% after allo-HSCT, respectively (**Figure 1**). The incidence of TRM and CIR after auto- and allo-HSCT was 0% and 19% and 27% and 10%, respectively (**Table 1**).<sup>26</sup>

In the attempt to identify the favored choice of transplantation in patients with APL in second CR, data related to 294 patients (79 of them with age < 20 years) receiving allo-HSCT (232 patients) and auto-HSCT (62 patients) were retrospectively analyzed to compare toxicity, survival outcome and impact of residual molecular disease pre-HSCT on the outcome. The use of ATO therapy prior to HSCT was also evaluated; no impact of ATO-containing vs non-ATO pre-HSCT therapy on the relapse risk after transplant was observed. In this large number of patients, specific data related to the younger patients are not available. However, the univariate analysis showed a good OS, DFS and TRM in auto transplanted patients; 5-year OS was 75% and 54% for auto- versus allo-recipients (**Figure 2, 3**). Disease-free survival (DFS) at five years also favored auto-HSCT (63% vs 50%) (**Table 1**). In both auto- and allo-HSCT, molecular or cytogenetically positive grafts were not associated with an increased risk of relapse and overall mortality.<sup>17</sup>

A large number of pediatric APL patients (95 children; aged 0-19) transplanted between 1990 and 2014 were identified in the Japan Society of Hematopoietic Cell Transplantation (JSHCT) registry.<sup>27</sup> Forty of them underwent auto- or allo-HSCT in first CR



**Figure 2.** Center for International Blood and Marrow Transplantation Research (CIBMTR). Treatment-related mortality in patients undergoing allogeneic and autologous transplant for acute promyelocytic leukemia in second complete remission.



**Figure 3.** Center for International Blood and Marrow Transplantation Research (CIBMTR). Overall survival in patients undergoing allogeneic and autologous transplant for acute promyelocytic leukemia in second complete remission.

and 55 in other settings (second CR: 41; third CR: 3 and no-CR: 11). HSCT was included in the front-line treatment before ATRA-era; it was subsequently adopted as a treatment for patients in second CR. Among the 40 patients transplanted in first CR, 19 underwent auto- and 21 allo-HSCT. Although there was no significant difference in 5-year OS (73% vs 86%) and DFS (68% vs 86%) between auto- and allo-HSCT groups, the 5-year cumulative incidence of relapse was significantly higher after auto-HSCT (32%) than after allo-HSCT (5%). Twenty-nine of the 42 patients treated in second CR underwent allo-HSCT and 13 auto-HSCT. There was no significant difference in 5-year OS and DFS between auto- and allo-HSCT groups (OS: 85% vs 78%; DFS

76% vs 75%). Both auto- and allo-HSCT were effective in pediatric APL patients in second CR. In this study, based on registry data, no information was available about the pre-transplant treatments or the PML-RARA molecular status at the time of transplantation. Even with intensive chemotherapy, achieving a CR was the most important factor in curing relapsed APL patients who had already received ATRA and ATO.

More recently, the 25-year Italian experience on the outcome of relapsed/refractory APL in children, adolescents and young adults has been reported.<sup>28</sup> Fifty-one patients (age < 18 years at initial diagnosis; median age 13.9 years at the time of the study), treated between May 1994 and May 2017 in 22 AIEOP (Associazione Italiana Ematologia e Oncologia Pediatrica) centers who experienced relapsed or refractory disease, were included in this study. All patients had received front-line ATRA and chemotherapy; salvage strategies were heterogeneous and, up to January 2008, were based on ATRA and intensive chemotherapy followed by allo- or auto-HSCT or different maintenance approaches for patients not eligible for transplant. After January 2008, when ATO was available for all patients, reinduction consisted of ATO + ATRA + gentuzumab ozogamycin (GO); patients with a persistent positive molecular disease underwent auto- or allo-HSCT. A total of 25 patients in second CR received HSCT as consolidation therapy, and more exactly: 18 patients, salvaged with ATRA + chemotherapy, were consolidated with either auto- (7 patients) or allo-HSCT (11 patients); 7 out of 18 patients who had received ATO+ATRA were consolidated with auto- (1 patient) and allo-HSCT (6 patients) (**Table 2**). The molecular status at transplant time was available in 18/25 patients, and all were negative. The univariate analysis for OS and EFS

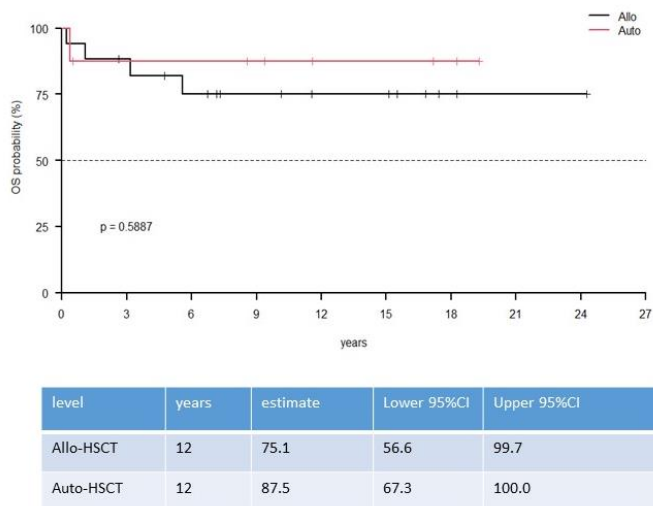
showed no significant difference between transplanted and non-transplanted patients (OS: HR 2.43; EFS: HR 1.10) and between those consolidated with auto- or allo-HSCT (OS 87.5% vs 76% and EFS 72.9% vs 70.6%) (**Table 1**) (**Figure 4, 5**). These data compared favorably with those reported in relapsed APL adults from the European Acute Promyelocytic Leukemia Group, comparing auto- and allo-HSCT. This study demonstrated the efficacy of auto-HSCT performed in molecular CR (**Figure 6**).<sup>29</sup>

In the pediatric age, based on literature data on relapsed APL, recommendations on APL salvage therapy were established by members with APL expertise from the North American Children's Oncology Group (COG) and the International Berlin-Frankfurt-Münster Study Group (I-BFM SG).<sup>13</sup> The quality of evidence for these recommendations was mainly derived from expert opinion, while a final agreement was by consensus. Several studies, mostly involving adults, had identified prognostic factors in patients with relapsed APL who underwent salvage therapy with or without HSCT.<sup>13,17,30,31</sup> Time to relapse (< 18 months from diagnosis), prior ATO therapy, and failure to clean PML-RARA transcript had an unfavourable impact on patients' outcomes. These factors can be useful to predict the risk of further relapse and consequently to guide which children can be treated with further differentiating agents and/or chemotherapy and who would benefit from either auto- or allo-HSCT. Therefore, treatment algorithms have been created, dividing patients according to time to relapse, previous ATO exposure and relapse site (**Figure 7**). According to these recommendations, for children with relapse occurring less than 18 months from initial diagnosis and with previous or no ATO exposure, auto-HSCT is planned only for those who achieve a second

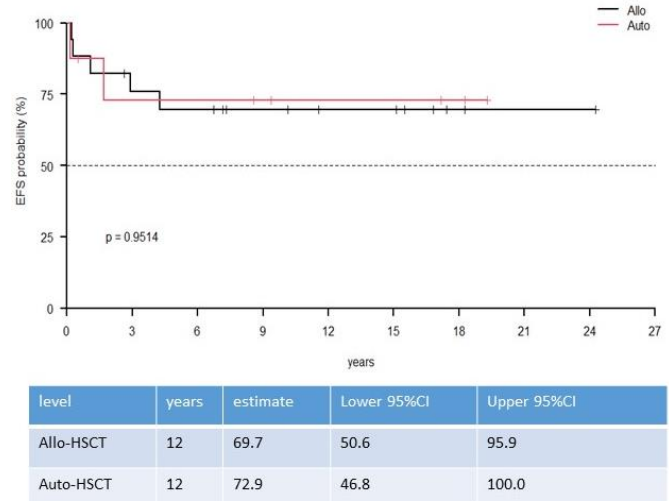
**Table 2.** Italian Experience. Patients with relapsed/refractory APL re-induced with ATRA + chemotherapy or ATO: outcome by type of consolidation.

1994-2008	Total *r/r **pts	Salvage Chemotherapy+ATRA^+ maintenance	Chemotherapy+ATRA+ ^^Allo- HSCT	Chemotherapy+ATRA+°Auto- HSCT
N. pts in °CR2	31	13	11	7
N. Relapses (months)	9	5 (median 20; range 5-47)	2 (38, 56)	2 (6, 25)
Deaths in °CR2	1	0	1	0
^^^CCR2 (months)	21	8 (median 135; range 20-258)	8 (median 219; range 87 -296)	5 (median 210; range 128-258)
2008-2017	Total r/r pts	Salvage §ATO/ATRA/§§GO	ATO/ATRA/±GO+Allo-HSCT	ATO/ATRA/GO+Auto-HSCT
N. pts in CR2	18	11	6	1
N. Relapses (months)	4	2 (15, 16)	1 (3)	1 (2)
Deaths in CR2	0	0	0	0
CCR2 (months)	14	9 (median 74; range 30-138)	5 (median 90; range 26-125)	0

\*r/r: relapsed/refractory; \*\*pts: patients; ^ATRA: All-trans retinoic acid; ^^Allo-HSCT: Allogeneic hematopoietic stem cell transplant; °auto-HSCT: autologous hematopoietic stem cell transplant; °CR2: Second complete remission; §ATO: Arsenic trioxide; §§GO: Gentuzumab-ozogamycin; ^^^CCR2: continuous complete second remission.

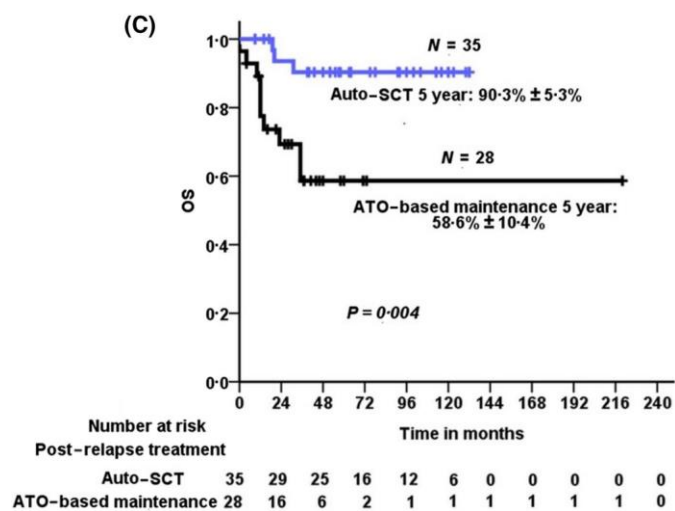


**Figure 4.** Overall survival for Italian children/adolescents undergoing allogeneic- or autologous-hematopoietic stem cell transplant in second complete remission.



**Figure 5.** Event-free survival for Italian children/adolescents undergoing allogeneic- or autologous-hematopoietic stem cell transplant in second complete remission.

molecular CR after induction and consolidation strategy.

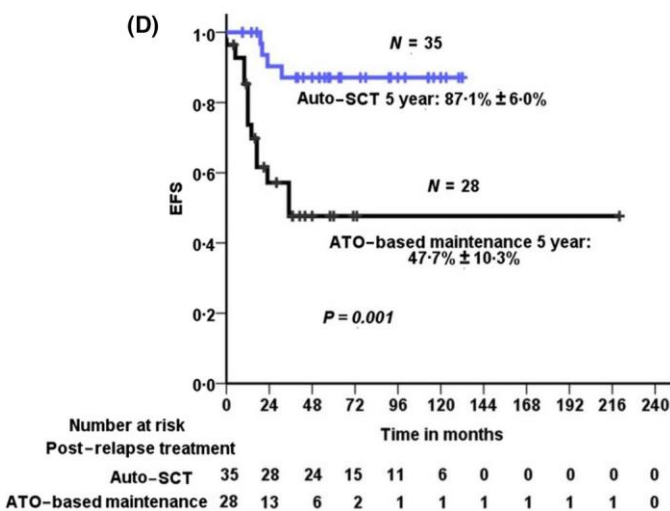


Stem cell mobilization and collection are obtained in these patients after a further high-dose cytarabine consolidation course. For the patients still PML-RARA positive at the end of consolidation, allo-HSCT is recommended after a further cycle of intensive therapy. ATO-naïve children with relapse occurring 18-36 months from initial diagnosis can be reinduced with ATO-ATRA and GO and proceed to allo-HSCT only if persistently PML-RARA positive at the end of consolidation. Children with prior ATO exposure and late relapse who clear PML-RARA transcript after four consolidation courses can be considered for auto-HSCT; for those still positive, allo-HSCT is planned after other intensive consolidation chemotherapy.

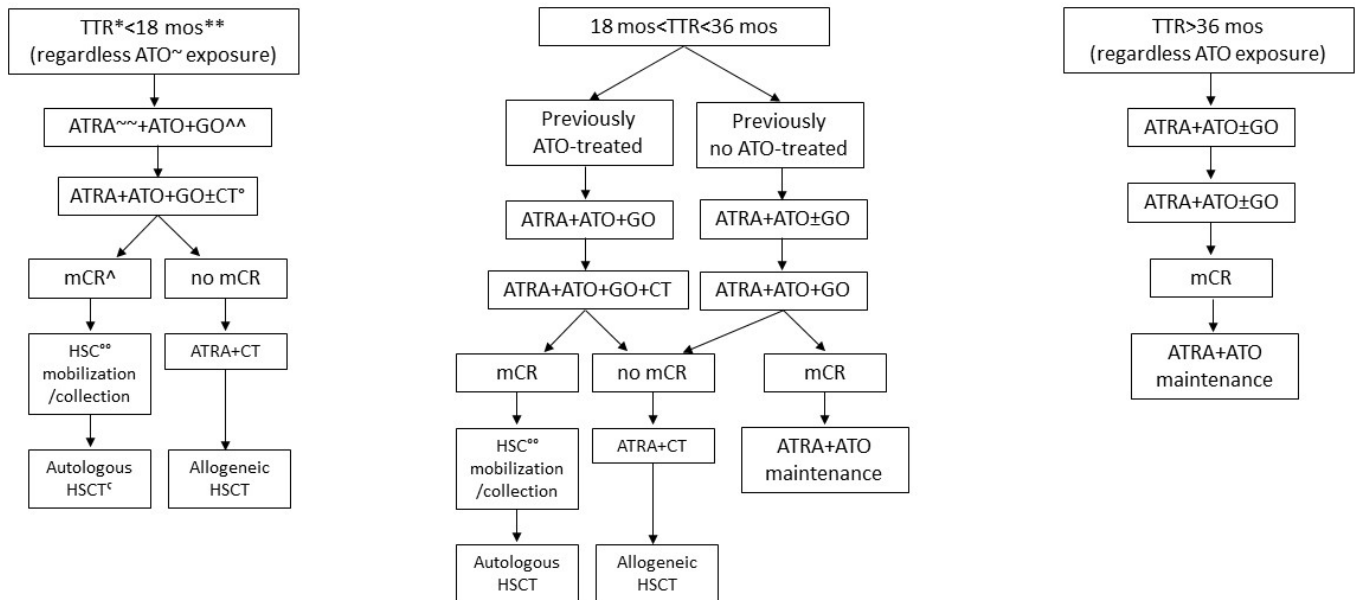
Regarding the conditioning regimen, no advantage has been shown for TBI in acute myeloid leukemia (AML), and in pediatric age, chemotherapy-only regimens should be used. There is no proven best chemotherapy conditioning regimen, though myeloablative regimens with busulfan and cyclophosphamide and therapeutic drug monitoring of busulfan levels are currently the standard of care. In pediatric AML, busulfan, cyclophosphamide and melphalan have been successfully employed; the choice is usually balanced between efficacy and toxicity with a careful evaluation of previous drugs that may contribute to the toxicity.

All these recommendations were made to assist in designing therapy for children with APL relapse; since APL patients are a heterogeneous population, these schemas may require modifications based on individual patients' characteristics and the resources available to the treating physicians.

**Very Late Relapse.** Only sporadic reports of adult and pediatric patients with very late relapse have been published. Very late relapse is defined as any relapse at hematological or molecular level, occurring > 36



**Figure 6.** C) Overall survival, D) Event-free survival of adult and pediatric patients with acute promyelocytic leukemia in second complete remission consolidated with autologous-stem cell transplant versus arsenic trioxide-based maintenance regimen.



**Figure 7.** Treatment algorithm for relapsed pediatric APL. \*TTR=time to relapse; \*\*mos=months; ~ATO=arsenic trioxide; ~ATRA=all-trans retinoic acid; ^mCR=molecular complete remission; ^^GO=gentuzumab ozogamicin; °CT=chemotherapy; °HSC=hematopoietic stem cells; ^HSCT=hematopoietic stem cell transplant.

months from diagnosis. The bone marrow and/or extra-hematological sites may be involved.

Although no standard of care for treating these relapses exists, drug resistance is unlikely in these patients, and, irrespective of front-line ATO therapy, salvage with ATO-based regimens remains effective; GO has also been demonstrated to be effective.<sup>31-35</sup> While the role of ATO in remission induction in these patients is well established, the benefit of consolidation HSCT is questionable for patients relapsing after a very prolonged first CR. The registry study of the European LeukemiaNet collecting and analyzing the results of 155 relapsed APL patients has clearly demonstrated the role of allo-HSCT as consolidation therapy for patients with either early or late relapse not achieving a molecular CR and suggested auto-HSCT as a suitable option for patients in second molecular CR.<sup>31</sup> However, the transplant options could be questioned for patients relapsing after a very prolonged first CR in whom continuing ATRA-ATO might be curative. Though limited to a small number of patients, a prolonged second molecular CR with ATO-based salvage therapy has been described in the literature.<sup>31-35</sup> ATO+ATRA combination in repeated consolidation courses, associated or not with GO, and PML-RARA quantitative monitoring, will probably contribute to avoiding HSCT in patients with very late relapse.

**Extramedullary Relapse.** Extramedullary relapse in APL can involve many sites but more frequently affects the central nervous system (CNS), skin or external auditory channel.<sup>35,36</sup> The best management of children with CNS relapse of APL remains to be determined, and the role of HSCT in isolated CNS relapse is still

controversial, although it was recommended by the European LeukemiaNet in 2009.<sup>14</sup> An extensive pediatric literature reports a very low incidence of isolated CNS relapse (1.39%).<sup>37</sup> Most CNS relapses are accompanied by evidence of molecular bone marrow disease and are significantly associated with high WBC counts and/or intracranial hemorrhage at diagnosis. There is a higher incidence of bcr3 PML-RARA isoform, expression of antigen CD56 on the leukemic cell surface, and microgranular M3 variant, presence of FLT3-ITD mutation and young age are more frequently associated with extramedullary APL relapse.<sup>37,38</sup>

ATO is currently the first-line therapy for refractory/relapsed APL and may also benefit patients with CNS relapse. ATO accumulates in epidermal tissues and penetrates the blood-brain barrier, reaching cerebral spinal fluid (CSF) levels up to 50% of serum levels; thereafter, therapeutic response at these sites is expected.<sup>39</sup> For CNS relapse, intrathecal chemotherapy in combination with/without ATO-ATRA has been described as a successful treatment of CNS relapse. Drugs with high CNS penetrance, such as high-dose cytarabine, have been used in CNS relapse, followed by auto-HSCT or cranial radiotherapy.<sup>40</sup> The need for radiotherapy is also questionable, although some centers still follow this approach. Allo-HSCT is also recommended for patients with an available HLA-identical donor by some experts, although auto-HSCT is preferred by others, owing to its lower TRM. For those patients with concomitant bone marrow molecular disease, achieving a molecular CR should be important for a successful outcome of auto-HSCT.

ATO alone or in combination with ATRA to treat non-CNS isolated extramedullary relapse is a reasonable

strategy.<sup>41</sup> HSCT is not recommended in these cases.

### Comments and Conclusions.

- The widespread clinical employment of ATO and ATRA combination in pediatric and adult APL has made relapse a rare event, especially in children
- HSCT has ceased to play any role in the first-line treatment, and it is relegated to consolidating patients in second complete remission or beyond after salvage treatment
- ATO is currently the first-line therapy for refractory/relapsed APL, but the optimal post-remission therapy in pediatric patients with second complete remission after either ATO or ATRA+chemotherapy remains undefined
- No significant differences in EFS and OS have been observed between auto- and allo-HSCT in the two largest pediatric series, including relapsed pediatric APL
- The molecular disease status at the time of transplant has emerged as an important prognostic variable
- In the attempt to assist in designing therapy for children with relapsed/refractory APL, recommendations from an international expert panel

have been published

- ATO-naïve children with late relapse (> 18 months from diagnosis) and those with very late relapse (> 36 months from diagnosis), regardless of ATO exposure, can be reinduced with ATO/ATRA associated or not with GO followed by ATO consolidation without HSCT
- ATO-naïve children with early relapse (< 18 months from diagnosis) and those with prior ATO exposure and early or late relapse (18-36 months from diagnosis) who clear PML-RARA after four salvage courses could be candidates to auto-HSCT
- Children with early relapse or primary refractory APL or ≥ second relapse or with the persistence of PML-RARA positivity after salvage treatment, ATO treated or not, should be considered for allo-HSCT consolidation

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