Review

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Hematopoietic Stem Cell Transplantation in Acute Promyelocytic Leukemia in the ATRA/ATO Era

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Simple Summary: Acute promyelocytic leukemia (APL) currently benefits from first-line treatment based on all-trans retinoic acid and arsenic trioxide, ensuring long-term complete responses for most patients. However, a proportion of 5-20% of patients relapse, and their long-term survival, even under the conditions of therapy with the mentioned drugs, is no longer so favorable, making necessary the association of a highly efficient consolidation. Current recommendations indicate hematopoietic stem cell transplantation as consolidation treatment in patients with relapsed APL who achieve a new complete remission. Our article aims to present the current data on the role of transplantation in APL and the still debatable aspects regarding this therapy, as well as the new data on possible alternatives to this type of treatment.

Abstract: Acute promyelocytic leukemia (APL) currently represents one of the malignant hemopathies with the best therapeutic responses following the introduction of all-trans retinoic acid (ATRA) and later of arsenic trioxide (ATO) treatment. As a result, patients with APL achieve long-term responses in a large proportion after first-line therapy, so that performing hematopoietic stem cell transplant as consolidation of first complete remission is no longer necessary. Even in the case of relapses, most patients obtain a new remission thanks to the therapy with ATO and ATRA, but to maintain it, a consolidation treatment as effective as possible is necessary. The experience accumulated from studies published in the last two decades shows the effectiveness of hematopoietic stem cell transplantation (HSCT) in improving the evolution of patients who achieve a new complete remission. Thus, the recommendations of expert groups indicate transplantation as consolidation therapy in patients with a second complete remission with the mention of the use of autologous HSCT in cases with complete molecular remission and allogeneic HSCT for patients with the persistence of minimal residual disease or early relapse. However, there is a variety of controversial aspects related to the role of HSCT in APL, from obtaining outcome data almost exclusively from retrospective studies and historical analyzes to questions related to the type of transplantation, the impact of minimal residual disease, conditioning regimens, or the role of other therapeutic options. All these questions justify the performance of controlled prospective studies in the following years.

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1. Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML), that represents 10–15% of newly diagnosed AML cases [1–3]. At onset it is characterized by abnormal white blood cells (WBC) counts with distinctive blast morphology, thrombocytopenia, coagulopathy, and tendency to severe bleeding which makes APL a medical emergency requiring prompt diagnosis and treatment [2,4]. APL is cytogenetically characterized by the presence of a balanced translocation that involves the retinoic acid receptor alpha (RARA) gene on chromosome 17 (17q21). In the vast majority of APL cases t(15;17) (q22;q12-21) is present, leading to the fusion of the promyelocytic leukemia (PML) gene on chromosome 15 with the RARA gene thus resulting in the formation of the PML–RARA fusion transcript. In rare cases, rearrangements of 17q21 lead to the fusion of RARA to alternative partner genes such as NPM (nucleophosmin) associated with t(5;17)(q35;q12-21), ZBTB16 (zinc finger and BTB domain containing protein 16) (former PLZF - promyelocytic leukemia zinc finger) with t(11;17)(q23;q21), NuMA (nuclear mitotic apparatus) t(11;17)(q13;q21) and other variants (14 variants known to date)[5]. The resulting RARA fusion disrupts normal RARA signaling leading to block in differentiation and maturation of myeloid cells, causing accumulation of immature promyelocytes in the bone marrow and peripheral blood. [2,6–8].

Introduction over the last decades of differentiating agents targeting the specific genetic aberration implicated in pathogenesis, like all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), has transformed APL into the most curable acute leukemia with almost 90% long-term survivor patients [2,4,9]. However, 5-20% of APL patients relapse after achieving initial remission [9,10] with a second relapse rate even higher (approximately 41– 48%) [11–13] which raises the problem of relapse therapy and post-remission treatment with the goal of maintaining a new remission for the longest possible period. Although the place of HSCT in the management of these patients is defined by current guidelines there are still various controversial aspects regarding its role in APL.

In our article we aim to provide an overview of the current available data on HSCT in APL patients by discussing aspects related to indications, type of transplant, stem cell source, donor selection, conditioning regimens, prognostic factors, impact of minimal residual disease and future perspectives.

2. Transplantation in newly diagnosed APL

According to the European Leukemia Net (ELN) guidelines, therapy for newly diagnosed patients consists of induction, consolidation, and maintenance treatment guided by risk stratification (high risk disease - WBC count >10 × 10^9/L, non-high-risk disease -WBC count ≤10 × 10^9/L respectively) [14]. Induction therapy consists of combinations of ATRA with ATO, ATRA with anthracycline-based chemotherapy or ATRA with ATO and chemotherapy depending on the risk stratification. Also, consolidation and maintenance are carried out in accordance with the category of risk (for non-high-risk patients – chemotherapy-free consolidation and no maintenance while for high-risk patients' consolidation with ATRA + chemotherapy is followed by maintenance) [14]. This therapeutic strategy leads to high complete remission (CR) rates over 90%, even 100% in some studies, along with high event free survival (EFS) rates (80-97%) and overall survival (OS) rates (93-99%) [2,15–17].

These very good results of first line therapy led to the decrease of the importance of HSCT in APL in CR1. Indeed, since the early era of ATRA therapy when HSCT was still largely used in CR1, along with the improvement of induction results and the introduction of ATO, the number of HSCT procedures has registered a steady decrease in CR1 APL patients [18–21]. Currently, the consensus expressed by the most recent recommendations and guidelines of ELN, the European Society for Blood and Marrow Transplantation (EBMT) and National Comprehensive Cancer Network (NCCN) is that HSCT is not recommended in CR1 in APL patients regardless of their risk stratification [14,22,23].

Although recent outcome data show that disease resistance has practically disappeared in almost all patients with genetically proven PML/RARA APL, achieving CR with current therapies, there are still reports of rare cases with molecular persistence of disease at the end of consolidation, that require immediate additional treatment, including HSCT if feasible [14].

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A special situation is that of the APL variants (APLv), among which of the 14 variants described so far, in 4 resistance or at least a low sensitivity to differentiation inducing agents has been reported: poor response of ZBTB16-RARA and STAT5b-RARA variants to both ATRA and ATO, 1 case of BCoR-RARA insensitive to ATO and 1 case of TBLR1-RARA variant insensitive to ATRA [14,24–27]. The outcome of these variants is associated with relapsed rates of 30-80% reported in several studies [28,29]. A recent study presented 24 cases of APLv followed over 12 years in several worldwide centers including 18 cases with ZBTB16-RARA, 3 STAT5B-RARA, and 1 each with PRKAR1A-RARA, NuMA-RARA, and FIP1L1-RARA rearrangements [5]. In this series there was no evidence of differentiation with ATRA and/or ATO in patients with either ZBTB16-RARA or STAT5B-RARA rearrangements and most of these patients received transplant-based treatment [5].

3. Relapsed APL

Regardless of the advances in APL therapy through the introduction of differentiation-inducing agents, there is still a proportion of 5-20% of cases that relapse [9–11]. In the great majority of cases relapse occurs during the first three years [2,30]. The incidence of relapses is lower in patients initially treated with ATRA + ATO compared to those treated with ATRA + chemotherapy [15–17]**.** Relapse is defined as hematological relapse by the reappearance of >5% abnormal promyelocytes in the bone marrow or molecular relapse defined as two successive PCR-positive assays, with stable or rising PML-RARA transcript levels detected in independent bone marrow samples analyzed in two laboratories. [10,20]. Early initiation of therapy, immediately after detection of molecular relapse, confers a better outcome than treatment after the appearance of frank hematological relapse [31,32], hence the recommendations to initiate preemptive therapy [14,23,33].

The molecular mechanisms leading to relapse are incompletely known, they may involve resistance to ATRA as a result of increased catabolism and decreased delivery to cell nucleus of ATRA, mutations in the ligand-binding domain of the RARA portion of the fusion protein, occurrence of additional mutations (e.g. Flt3) or additional chromosomal abnormalities as well as mutations in the PML domain with decreased sensitivity to ATO and they might differ depending on the initial therapy and the time of relapse [34–37]. A study conducted on 45 patients with relapse/progression after ATRA + chemotherapy initial therapy, mutations in the ligand binding domain of PML-RARA were found in 18 cases (40%) of which 11 cases with progression during ATRA therapy and 7 with relapse after the end of ATRA therapy [34]. Another study of 35 patients with relapse after ATO identified point mutations within the B2 domain of PML in 9 patients with ATO-resistant disease and 7 patients with ATO-resistant disease simultaneously harbored RARA mutations. In this study, patients having only RARA mutations responded to ATRA+ATO therapy, while none with both PML and RARA mutations responded [37].

According to this data, current guidelines provide that therapy for molecular or hematologic relapse should be chosen considering the previously used first-line treatment. However, the proposed therapies differ between the recommendations of various expert groups. Thus, the ELN guideline recommends a "cross-therapy" scheme: APL patients relapsing after ATRA + chemotherapy should be treated with an ATRA + ATO-based approach as salvage therapy until achievement of minimal residual disease (MRD) negative status based on RT-PCR, whereas those relapsing after ATO-based therapy, should receive ATRA + chemotherapy. Patients with late relapse (CR1 duration > 2 years) could be excepted from crossing over to a different treatment of relapsed [14]. On the other hand, in the NCCN guide, the limit between early and late relapses is set at 6 months. Patients with early relapse after initial therapy with ATRA+ATO will be treated with regimens based on anthracyclines or gemtuzumab-ozogamicin (GO) +ATRA, and those with initial treatment with ATRA + chemotherapy will receive ATO ± ATRA±GO. Patients with late relapse after first-line therapy with ATO, will be treated at relapse with ATO±ATRA±chemotherapy or GO [23]. Studies analyzing treatment with ATO in relapsed APL cases following initial anthracycline-based treatment showed high CR2 rates of 80–85% or higher [11,13]. Data about treatment outcome with ATRA + chemotherapy in cases with relapse after ATRA + ATO initial therapy are scarcer with molecular CR reported rates of 91% and 0.74 probability of disease-free survival at 4 years [38], so

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that the treatment recommendation was based on an expert consensus rather than on data from clinical experience [39]. However, recent data showed that in younger APL patients relapsed after frontline ATO reinduction with an ATO-based regimen could be effective regardless of time elapsed from first complete remission [39]. The second relapse rate is also relatively high even after ATO based therapy (approximately 41–48%) [2,13]. Thus, the main objective of therapy in relapsed APL is the achievement of molecular remission as a bridge to an efficient consolidation therapy [10,14].

The choice of the appropriate post-remission therapy in CR2 is dependent on factors specific to the patient (age, comorbidities, donor availability) or disease specific variables (depth of response – molecular status at the end of treatment, duration of first remission, presence of mutations).

At the present time, most expert groups suggest HSCT as the best consolidation therapy after salvage therapy for relapsed APL. Both ELN and NCCN guidelines recommend autologous HSCT as the first choice for eligible patients achieving second molecular remission, while patients failing to achieve molecular remission should undergo an allogeneic HSCT [14,23]. The eighth report of the EBMT covering indications for hematopoietic cell transplantation recommends autologous and allogeneic transplantation from matched sibling donor as standard of care for APL in molecular CR2 [22].

These recommendations derive from published data on the management of relapsed APL suggesting a better survival after consolidation with HSCT. These available data regarding the role of autologous and allogeneic HSCT following relapse in APL are mainly from retrospective single center studies, uncontrolled comparisons and registry data analyzes, reporting outcomes with different types of induction and salvage therapies, conditioning regimens, and various follow-up periods [11,13,39–44] (Table 1). Thus, the earliest information comes from studies analyzing the outcome with or without HSCT in relapsed APL patients treated with ATRA+ chemotherapy. A retrospective analysis of the European Acute Promyelocytic Leukemia Group published in 2005 performed on 122 patients with CR2 after ATRA + chemotherapy showed a superior relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS) at 7 years in the autologous HSCT (auto-HSCT) group (79.4%, 60.6% and 59.8%) and allogeneic HSCT (allo-HSCT) group (92.3%, 52.2% and 51.8%) compared to patients not receiving transplantation (38%, 30.4%, and 39.5%, respectively) [40]. A retrospective analysis of the JALSG APL97 study reported the outcome of 57 APL patients with CR2 after ATRA based therapy in APL97. The 5-year EFS rate, OS rate and cumulative incidence of relapse (CIR) were 50.7%, 77.4% and 51.0% in the non-HSCT group (30 patients), 41.7%, 83.3% and 58.3% in the auto-HSCT group (6 patients) and 71.1%, 76.2% and 9.8% in the allo-HSCT group (21 patients), respectively [41]. Subsequently, several studies comparing the evolution with and without HSCT in patients with relapsed APL who received salvage therapy with ATO were published [11,13,39,42,44].

Table 1. Post-remission therapy in relapsed APL – comparison of transplantation vs. non-transplantation.

Study	Study period/ type	Relapse therapy	Post-remission treatment	No.	RFS	EFS	OS	RR
de Botton et al., 2005 [40]	1992-2001 Retrospective Multicentric	ATRA+ CT	Auto	50	79%(7y)	61%(7y)	60%(7y)	
			Allo	23	92%(7y)	52%(7y)	52%(7y)	
			Non-HSCT	49	38%(7y)	30%(7y)	40%(7y)	
Thirugnanam et al. 2009 [42]	1998-2006 Retrospective Unicentric	ATO - based	Auto	14		83%(5y)	100%(5y)	7%(7y)
			Non-HSCT	19		34%(5y)	39%(5y)	63%(7y)
Pemmaraju et al., 2013 [43]	1980-2010 Retrospective Unicentric	Various	Auto	10		69%(7y)	86%(7y)	
			Allo	17		41%(7y)	49%(7y)	
			Non-HSCT	16		NA	40%(7y)	
Fujita et al., 2013 [41]	1997-2002 Retrospective Multicentric	ATRA+ CT	Auto	6		42%(5y)	83%(5y)	58%(5y)
			Allo	21		71%(5y)	76%(5y)	10%(5y)
			Non-HSCT	30		45%(5y)	75%(5y)	51%95y)
Lengfelder et al. 2015 [13]	2003-2011 Retrospective	ATO - based	Auto	60			77%(3y)	37%(3y)
			Allo	33			79%(3y)	39%(3y)

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	ELN Registry		Non-HSCT	55			59%(3y)	59%(3y)
Ganzel et al., 2016 [44]	2000 -2011 Retrospective Registry data	ATO or CT based	Auto Non-HSCT	140 67			78%(5y) 42%(5y)	
Fouzia et al., 2021 [39]	1998-2015 Retrospective Unicentric	ATO - based	Auto Non-HSCT	35 28		87%(5y) 48%(5y)	90%(5y) 59%(5y)	
Min et al., 2022 [11]	2000 – 2019 Retrospective Unicentric	ATO or CT based	Auto Allo Non-HSCT	12 6 19	66%(3y)* 50%(3y) 44%(3y)		75%(3y) 66% (3y) 65%(3y)	41%(3y) 0% (3y) 50%(3y)

CT – chemotherapy, ATO – arsenic trioxide, RFS – relapse free survival, EFS- event free survival, OS – overall survival, RR – relapse rate, HSCT – hematopoietic stem cell transplantation; * DFS - disease free survival.

A retrospective ELN study analyzing the outcome of 155 patients treated with ATO in first relapse showed a favorable significant prognostic impact of autologous and allogeneic HSCT on OS and leukemia-free survival compared to patients without HSCT [13]. A retrospective study on data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and EBMT registries, analyzed 207 patients with relapsed APL receiving ATO and compared the outcome of 67 patients receiving ATO alone and 140 with auto-HSCT. At 5 years, OS was 42% and 78% for the ATO-only and auto-HSCT groups, respectively (P <0.001) [44].

As data from published studies and expert groups recommendations indicate a better outcome of relapsed APL patients with HSCT consolidation there are still some debatable aspects mainly due to insufficient or conflicting data and lack of prospective, controlled studies: influence of pre-transplant therapy, type of transplant, stem cell source, best type and timing of mobilization and stem cell harvesting for auto-HSCT, donor type, conditioning regimen, influence of minimal residual disease status prior to HSCT, prognostic factors, possible alternatives to HSCT.

Pre-transplant salvage therapy. A limited amount of information is available regarding the impact of the type of pre-transplant therapy on patients' outcome and with discordant results. A retrospective multicentric study on 58 patients undergoing autologous HSCT for APL at 21 institutions in the United States and Japan reported significantly longer times to neutrophil recovery (median 12 days vs 9 days, P<0.001) as well as lower median viable post-thaw CD34+ cell recovery of cryopreserved autologous stem cell products from patients with prior treatment with ATO suggesting that that ATO exposure prior to CD34+ cell harvest has deleterious effects on hematopoietic recovery after autologous HSCT. In this study relapse-free survival (RFS) and OS were shorter in patients receiving ATO prior to stem cell collection [45]. In an analysis of data from CIBMTR/EBMT registries, in the auto-HCT group, 79 patients received ATO as part of the salvage therapy before transplant and 54 received ATRA + chemotherapy with similar OS of the two groups (P=0.274) [45]. In a large retrospective study of the CIBMTR data on 62 patients with auto-HSCT and 232 patients with allo - HSCT from 79 centers in 18 countries during the years 1995-2006, there was no impact of ATO pre-transplant therapy on the risk of relapse after HSCT evaluated by univariate and multivariate analysis [46]. Another retrospective registry-based study from the Japanese Transplant Registry Unified Management Program involved 198 patients with APL who underwent auto - HSCT during second CR2 from 1995 to 2012. Patients transplanted after ATO-based therapy had significantly better RFS, OS and CIR compared to those treated without ATO, whereas non-relapse mortality did not differ between the two groups suggesting that the introduction of ATO may result in significant improvements in overall outcomes for relapsed APL patients undergoing auto - HSCT during CR2 [47].

Another aspect is the lack of consensus regarding the best therapy prior to HSCT event in the ATO era. In the aforementioned Japanese study, patients received three courses of ATO therapy prior to the peripheral blood stem cells (PBSC) collection [47]. In the ELN study, induction ATO monotherapy was followed by a second ATO or ATRA+ATO course as consolidation [13]. Other authors used ATO monotherapy until CR2 was achieved followed by at least two consolidation cycles

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with ATO [11]. No available data can indicate so far if two courses are sufficient or more therapy is needed prior to HSCT or whether MRD negativity needs to be achieved in the bone marrow [48].

Type of transplant. An important aspect in conducting efficient consolidation therapy after obtaining CR2 is the choice of the appropriate type of transplant. Generally, auto-HSCT is associated with a better safety profile - lower non-relapse mortality (NRM), absence of graft-versus-host disease (GVHD), and better of the quality of life (QOL) - counterbalanced by a higher risk of relapse, while the performance of allo -HSCT is followed by a lower relapse rate (RR) but at the price of higher NRM and deterioration of QOL caused by treatment complications including GVHD [48,49]. Comparative data of auto - vs. allo - HSCT in the setting of CR2 APL patients are available from a reduced number of retrospective uncontrolled studies and registry data analyzes (Table 2) [11,13,18,20,40,41,43,46,50–52]. Most published data provide support in favor of autologous HSCT mainly due to better results in terms of OS [11,40,43,49,50,50] and NRM [20,46,51,52], even if some studies revealed significantly higher RR [11,41] when compared to allogeneic transplant. In the largest study published so far, data from the EBMT Registry including 228 patients with allo-HSCT and 341 patients with auto-HSCT were analyzed in terms of leukemia free survival (LFS), OS, RR and NRM. The 2-year probabilities of LFS, OS, RR, and NRM were 75%, 82%, 23%, and 3% for autologous HSCT and, 55%, 64%, 28%, and 17% for allogeneic HSCT respectively. In the multivariate analysis, LFS, OS, and NRM were better for patients undergoing auto-HSCT than for those undergoing allo-HSCT [52].

Table 2. Comparative results of autologous vs. allogeneic HSCT in APL patients in CR2.

Study	Study period/type	Relapse therapy	HSCT type	No.	RFS	EFS	OS	RR	NRM
de Botton et al., 2005 [40]	1992-2001 Retrospective Multicentric	ATRA+CT	Auto Allo	50 23	79%(7y) 92%(7y)	61%(7y) 52%(7y)	60%(7y) 52%(7y)		
Pemmaraju et al., 2013 [43]	1980-2010 Retrospective Unicentric	Various	Auto Allo	10 17		69%(7y) 41%(7y)	86%(7y) 49%(7y)		
Fujita et al., 2013 [41]	1997-2002 Retrospective Multicentric	ATRA+CT	Auto Allo	6 21		42%(5y) 71%(5y)	83%(5y) 76%(5y)	58%(5y) 10%(5y)	
Lengfelder et al. 2015 [13]	2003-2011 Retrospective Multicentric	ATO - based	Auto Allo	60 33			77%(3y) 79%(3y)	37%(3y) 39%(3y)	
Min et al., 2022 [11]	2000 – 2019 Retrospective Unicentric	ATO or CT based	Auto Allo	12 6	66%(3y)* 50%(3y)		75%(3y) 66%(3y)	41%(3y) 0% (3y)	
Kohno et al. 2008 [50]	1999-2004 Retrospective Multicentric	Various	Auto Allo	15 13	69%(4y) 46%(4y)		76%(4y) 46%(4y)	21%(4y) 9%(4y)	
Holter Chakrabarty et al,2014 [46]	1995-2006 Retrospective Registry data	non-ATO / ATO based	Auto Allo	62 232	63%(5y) 50%(5y)		75%(5y) 54%(5y)	30%(5y) 18%(5y)	7%(5y) 31%(5y)
Alimoghaddam et al.2011 [51]	1989-2011		Auto Allo	11 29		52%(5y) 62%(5y)	47%(5y) 66%(5y)		0%(5y) 21%(5y)
Sanz et al., 2007 [20]	1993-2003	ATRA+CT	Auto Allo	195 137	51%(5y) 59%(5y)			37%(5y) 17%(5y)	16%(5y) 24%(5y)
Sanz et al., 2021[52]	2004-2018 Retrospective Registry data		Auto Allo	341 228		75%(2y) 55%(2y)	82%(2y) 64%(2y)	23%(2y) 28%(2y)	3%(2y) 17%(2y)

CT – chemotherapy, ATO – arsenic trioxide, RFS – relapse free survival, EFS- event free survival, OS – overall survival, RR – relapse rate, HSCT – hematopoietic stem cell transplantation; * DFS - disease free survival.

In addition to data from retrospective studies, evidence of the outstanding efficacy and feasibility of auto-HSCT after induction and consolidation with ATO in relapsed APL was provided by a prospective study on 23 patients who underwent auto-HSCT demonstrating 5-year EFS, OS and NRM rates of 65% ,77%, and 0% respectively [53].

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Currently, autologous HSCT is widely accepted as the preferred treatment for patients with relapsed APL who have obtained CR, particularly when the patients are in molecular CR [14,23].

Stem cell source in auto-HSCT. Stem cell harvesting. Most studies on auto-HSCT reported as main stem cell source peripheral blood [11,13,21,39–44,46,47,51–53]. Peripheral blood stem cells (PBSC) were harvested after obtaining remission, assessed by morphological and karyotypic examination [40] or in most cases after molecular examination and achievement of MRD negativity [39–41,53]. Mobilization of PBSC was performed with granulocyte colony-stimulating factor (G-CSF) (variable dose – 5 or 10 μg/kg/day) in steady-state, or after chemotherapy (various regimens) [39–42,53]. There are practically no data regarding comparative results on mobilization therapy except occasional observations in a few studies: in the Japanese phase 2 prospective trial on auto-HSCT, PBSC harvest after high-dose cytarabine chemotherapy is presented as part of the sequential treatment of relapsed APL that lead to high efficacy in this setting [53]; in an Indian study including 35 patients, with PBSC collection after mobilization with G-CSF (10 μg/kg/day for 4 days) following ATO-based induction therapy, 37,1% of patients required a second-day harvest to achieve target stem cell dose [39].

There are few data on the impact of ***stem cell source in auto-HSCT,*** the very few studies that analyzed the influence of stem cell source on outcome showing no statistical differences [20,21]. Yet, there are some observations regarding the difference of outcome after auto-HSCT of bone marrow stem cells or PBSC in MRD positive cases. An earlier Italian prospective study enrolled 7 patients with detectable MRD before auto-HSCT and all 7 experienced early relapses after performing bone marrow stem cell transplantation [54]. Data from an observational study from the CIBMTR included 6 patients with positive MRD before autologous HCT having similar DFS and OS with 35 patients with negative MRD [46]. A large retrospective study of the Japanese Society for Hematopoietic Cell Transplantation reported 35 patients with positive MRD and 293 MRD-negative before performing auto-HSCT using mainly PBSC, with no association between MRD status and TRM, relapse, and OS rates [21]. Another recent analysis of data collected from the Japanese Society for Transplantation and Cellular Therapy and the Japanese Data Center for Hematopoietic Cell Transplantation between 2006 and 2019 on 296 patients with PBSC auto-HSCT included 21 cases with detectable MRD. In this study MRD positive status had no significant impact on outcome [55]. Some authors speculated that PBSC auto-HSCT could be feasible in patients with PML-RARA positive bone marrow due to several mechanisms: effective eradication of residual disease in vivo, preferential mobilization into the autograft of short-term repopulating cells, but too few leukemia stem cells to induce relapse, the non-clonogenic nature of the PML/RARA-positive cells present in the graft or a modest purging effect of cryopreservation on unstable leukemic clones [18,21,46,55,56]. These aspects should be interpreted with great caution due to the small number of cases, retrospective collection of PML-RARA results and lack of standardization of the assay [21,46,55]. However, current guidelines recommend auto-HSCT as the first choice for patients achieving second molecular remission, while patients failing to achieve molecular remission should undergo an allo-HSCT [14,23].

The results of ***allogeneic HSCT***, despite providing a strong antileukemic effect through pre-transplantation conditioning therapy and the post-transplantation immunologic graft-versus-leukemia (GVL) effect, are undermined by the association of complications impacting QOL and especially by the increased risk of NRM [55]. In the context of APL patients in CR2 with better reported outcome after auto-HSCT, the high toxicity associated with allo-HSCT is less acceptable, recommending this procedure for selected patients with reduced benefit from auto-HSCT, such as those who cannot achieve CR, failing to achieve MR and/or relapsing after auto-HSCT [10,14,23,57]. Data regarding the results of allo-HSCT are provided by a small number of studies, very few of which have enrolled significant numbers of patients (Table 2). A survey of the EBMT activity in APL patients between 1993-2003 analyzed 137 patients receiving allo-HSCT in CR2 with 5-year LFS, RR and TRM of 59%, 17% and 24% respectively [20]. Data reported to CIBMTR from 1995 to 2006 included 232 patients receiving allo-HSCT in CR2 with results inferior to auto-HSCT (5-year EFS, OS, RR and TRM of 50%, 54%, 18% and 31% respectively) [46]. An analysis of EBMT transplant activity between 2004 and 2018 reported 228 patients with allo-HSCT with 2-year survival results inferior to those of auto-

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HSCT [52]. A large retrospectively analysis on Japanese nationwide transplantation registry data of patients with relapsed APL receiving exclusively allo-HSCT between 2006 and 2020, reported 195 patients including 69 who underwent transplantation in non-CR and 55 who relapsed after prior auto-HSCT with a median duration of follow-up of 5.4 years. The 5-year OS rates for patients with allo - HSCT in CR and non-CR were 58% and 39%, respectively if they did not receive a prior auto-HSCT. In the patients relapsing after an auto-HSCT, the 5-year OS rate was 47% for those with allo - HSCT in CR and 6% for those transplanted without achieving CR (p = 0.001). The conclusion of the study was that allo-HSCT is effective in selected relapsed APL patients with less expected benefit after auto-HSCT. A particularly dismal outcome is reported for patients relapsed after auto-HSCT failing to obtain further CR [57].

In the setting of allo-HSCT, ***the stem cell source*** varied, some groups using mainly bone marrow (proportions ranging from 64% to 87%) [20,40,41,46,50] while other used PBSC in most patients (53% - 79% of patients) [43,52,58]. Only one study reported that the use of mobilized PBSC was associated with decreased TRM in patients receiving allo-HSCT in CR2 (p=0.008) [20]. There were no other differences of outcome associated to stem cell source reported by other studies.

Donor type. Most studies on allo-HSCT in APL patients reported the use of stem cells from matched sibling donors (MSD) in a much higher proportion than that used in other types of leukemia, with percentages varying between 38-100% [18,20,40–43,46,50–52,58]. Some earlier studies even established as inclusion criteria the achievement of allo- HSCT from MSD [20,51]. In more recent studies the proportion of unrelated donors and alternative donors is higher, probably reflecting the current trends and advances in survival following the use of these types of donors [46,52,57]. The EBMT Registry data analysis included as donor type 130 MSD (57%), 83 matched and mismatched unrelated (36%), 4 haploidentical donors (2%), 5 cord blood units (2%) and 6 cases receiving stem cells from other relative (2%) [52]. In the study from the Japanese nationwide transplantation registry, donor sources included 48 related donors (HLA-matched in 39), 89 unrelated donors (HLA-matched in 68), and 58 single-unit umbilical cord blood (all HLA-mismatched). There were no significant differences regarding OS, relapse or NRM related to donor type [57].

Conditioning treatment. In the setting of ***auto-HSCT***, most studies reported the exclusive use of myeloablative conditioning (MAC) regimens [13,41–43,47,50,53]. Only 2 studies, analyzing the data from the CIBMTR Registry and from the EBMT Registry reported 8% and respectively 14% of cases receiving reduced intensity conditioning (RIC) [46,52]. In the majority of studies on auto-HSCT, chemotherapy-based conditioning was preferred [20,21,42,43,47,50–53,55]. Most groups preferred BU/CY as conditioning therapy [20,42,43,50–52] except some Japanese studies in which BU/MEL was more frequently used [21,47,53,55]. Moreover, the Japanese authors found some correlations between the conditioning regimes used and the outcome of patients with auto-HSCT. An analysis of the 25-years experience (1992-2006) of the JSHCT on auto-HSCT in APL patients showed that conditioning with BU/MEL had a protective effect against relapse (p= 0.018) [21]. Another study of prognostic factors in a series of 296 patients with APL performing auto-HSCT during second or subsequent complete remission (CR2+) between 2006 and 2019, showed that conditioning regimens not including busulfan were significantly associated with a shorter RFS (univariate analysis) and higher risk of NRM (multivariate analysis) [55]. Three studies reported preferential TBI-based conditioning for auto-HSCT [40,41,46]. A retrospective analysis of the European APL Group reported twice as many relapses in patients receiving CY-TBI conditioning compared to those who received BU/CY (p= 0.45) and concluded that BU/CY conditioning regimen was at least as effective as the CY-TBI conditioning regimen, suggesting that TBI might be avoided in case of auto-HSCT in APL [40]. In the ***allo-HSCT*** setting the use of TBI was preferred in the European APL Group analysis [40], the Japan Adult Leukemia Study Group APL97 report [41] and another Japanese study [50] while non-TBI-based conditioning was preferred in the most recent EBMT Registry report [52] and other studies [43,51]. The equal use of TBI- and non-TBI-based conditioning was reported by the CIBMTR Registry [46] and by the 2007 EBMT data report [20]. No significant comparative data between conditioning regimens were reported.

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The ***influence of minimal residual disease status prior to HSCT*** on outcome in the setting of patients with APL in CR2 was reported by several studies with conflicting results. Initial results on MRD impact were reported by Meloni *et al.* in a prospective study which enrolled 7 patients with detectable MRD before auto-HSCT followed by early relapses in all cases after using bone marrow cells for transplantation [54]. Several large retrospective studies including ELN and EBMT registries data analysis and a multicentric Italian study showed significant impact of pre-transplant MRD status on outcome after HSCT especially in the setting of allo-HSCT (Table 3) [13,52,58]. Other studies showed no influence of pre-HSCT MRD positive status on relapse, treatment failure or survival in allo-HSCT and, surprisingly, also in auto-HSCT [21,41,46,47,55]. It is worth mentioning that in these latter studies used PBSC as compared to the study of Meloni *et al.* in which the stem cell source was represented by bone marrow, bringing into discussion the possibility of performing PBSC auto-HSCT in patients with MRD positivity. Possible mechanisms explaining these differences are mentioned above. Nevertheless, current guidelines recommend autol-HSCT as the first choice for eligible patients achieving second molecular remission, while patients failing to achieve molecular remission should undergo an allo-HSCT [14,23].

Analysis of ***factors influencing outcome*** in the HSCT setting were reported by several retrospective studies (Table 3) [13,20,21,39,41,44,46,47,52,55,58]. The prognostic factors identified by most studies were CR1 duration [13,39,44,46,55], time from diagnosis to transplant [20,52], age [21,41,46,52] and order of remission (CR2 vs. CR≥3) [55,58].

Table 3. Prognostic factors and influence of MRD on post-transplant outcome in APL relapsed patients.

Study	Study period/type	HSCT type	Factors influencing outcome	Data on MRD status /impact on outcome
de Botton et al., 2005 [40]	1992-2001 Retrospective Multicentric	Auto Allo		Auto-HSCT - Superior 7y RFS, EFS, OS in patients with mCR compared to patients lacking molecular analysis (p=NS)
Ramadan et al., 2012 [58]	2000-2010 Retrospective Multicentric	Allo	CR 2 vs CR3+ for OS (p=0.05)	mCR prior to allo-HSCT – better OS (p=0.03), lower CIR (p=0.3)
Ganzel et al., 2016 [44]	2000 -2011 Retrospective Registry data	Auto	CR1 duration for OS (p=0.001), DFS (p=0.002), multivariate (p<0.001) Extramedullary disease - on OS (p=0.046), NS in multivariate analysis	
Fujita et al., 2013 [41]	1997-2002 Retrospective Multicentric	Auto Allo	age at CR2 ≥ 40 years (p=0.006)	Auto-HSCT - pre-transplant MRD had no predictive significance with respect to relapse
Lengfelder et al. 2015 [13]	2003-2011 Retrospective Multicentric	Auto Allo	CR1 duration ≥ 1,5 years (p=0.006) No negative impact of extramedullary disease on transplant outcomes	mCR2 before HSCT (p<0.001) (univariable and multivariable analysis)
Holter Chakrabarty et al,2014 [46]	1995-2006 Retrospective Registry data	Auto Allo	age > 40 years for DFS (p=0.005), OS (p<0.001) CR1 < 12 months on OS (p=0.021)	No influence of pre-HSCT MRD positive status on relapse, treatment failure or survival in auto- and Allo-HSCT
Sanz et al., 2007 [20]	1993-2003 Retrospective Registry data	Auto Allo	<u>Auto-HSCT</u> Year of HSCT for LFS (p=0.05) Interval from diagnosis to HSCT > 18 months for LFS (p=0.0001), TRM (p=0.0016) <u>Allo-HSCT</u> Year of HSCT for RI (p=0.0004), TRM (p=0.03)	

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			WBC at diagnosis for RI (p=0.008) Source of HSC for TRM (p=0.008)	
Sanz et al., 2021[52]	2004-2018 Retrospective Registry data	Auto Allo	Age (p=0.002) Time diagnosis to HSCT (p=0.006)	negative MRD before allo-HSCT ~ better 2y OS (p=0.001), 2y LFS (p=0.002)
Fouzia et al., 2021 [39]	1998-2015 Retrospective Unicentric	Auto	CR1 duration (p=0.025)	
Yanada et al., 2020 [21]	1992-2016 Retrospective Multicentric	Auto	HSCT period for RI (p=0.014) Age ≥ 50 years for NRM (p=0.007) Male vs female for NRM (p=0.009)	No association between MRD status and TRM, relapse, and OS rates
Yanada et al., 2022 [55]	2006 - 2019 Retrospective Registry data	Auto	CR1 duration ≥ 2 years for RFS (p=0.002) CR3+ vs CR2 for NRM (p=0.036)	MRD status - not predictive for survival outcomes
Yanada et al., 2017 [47]	1995-2012 Retrospective Multicentric	Auto	PS 0 vs ≥ 1	pre-transplantation PML-RARA status - not predictive for outcomes

CR- complete remission, mCR- molecular complete remission, RFS – relapse free survival, EFS- event free survival, LFS – leukemia free survival, OS – overall survival, RR – relapse rate, HSCT – hematopoietic stem cell transplantation; CIR- cumulative incidence of relapse, TRM – transplant related mortality, RI- relapse incidence, NRM – non-relapse mortality, MRD – minimal residual disease, WBC – white blood cells, PS- performance status, NS- non-significant.

Consolidation therapies as alternative possibilities to HSCT. Although consolidation with HSCT shows improved outcome it does appear that a significant subset of patients could experience long-term survival with ATO-based post remission therapy [59]. An interesting set of data comes from studies that enrolled patients with relapsed APL who obtained a second molecular CR, who were offered auto-HSCT but who could not continue with this procedure for non-medical reasons, usually because of financial constraints or patients' choice and who received ATO-based consolidation. An Indian study included 63 patients with CR2 and negative MRD of which 28 opted against auto-HSCT and received ATO-based maintenance therapy for 10 days/month for 6 months. For these patients OS and EFS (58,6% and 47,4% respectively at 5 years) were inferior compared to the auto-HSCT group but showing that for some patients ATO maintenance can generate long term survival [39]. A unicentric Korean study showed no significant differences in survival outcomes between 19 patients receiving ATO-based post CR therapy, 12 patients with auto-HSCT and 6 with allo-HSCT, suggesting that ATO-based post remission therapy is effective in patients achieving molecular CR2[11]. A report NCRI AML Working Group on the long-term follow-up of the AML17 trial included 31 APL patients achieving molecular CR2 of which 18 were treated with ATO+ATRA alone without transplant or consolidation chemotherapy and 14 remained in molecular remission after a 5-year follow-up [60].

Other options investigated by several studies are single agent GO [61], tamibarotene alone or in combination with ATO [62,63], venetoclax combinations [64–66], combination of ATO, ATRA, mitoxantrone and bortezomib [67] as well as the use of oral ATO [68,69]. Conducting prospective controlled studies is necessary to address the role of these various therapeutic options.

3. Conclusions and Future Perspectives

Due to the very good results obtained with ATO and/or ATRA therapy of newly diagnosed APL cases, HSCT is no longer indicated in front-line treatment, excepting extremely rare cases of persistent MRD or APL variants. At the present time, the main indication for HSCT is in relapsed APL as consolidation after obtaining the second remission. Current guidelines recommend autologous transplantation for patients who achieve a second molecular remission, while allogeneic

transplantation should be used in cases with persistent MRD after salvage therapy, those with short CR1 or relapses after autologous HSCT. Controlled prospective studies are needed in the future to clarify the existing controversies.

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