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Autologous Stem Cell Transplantation for Acute Myeloid Leukemia

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1. Introduction

In the majority of patients, the therapy of acute myeloid leukemia (AML) has a curative intent and includes two phases, i.e. induction and consolidation. The former aims at complete remission (CR) achievement, the latter at the eradication of residual leukemic cells, which are undetectable at morphologic examination of bone marrow after induction therapy in patients in CR. Current induction regimens, conventionally based on the combination of daunorubicin and cytarabine result in CR rates of 60 – 70% of AML patients younger than 65 years; in order to improve both CR rate and quality, different studies tested alternative anthracyclines [1]-[5], higher schedules of Ara-C[6]-[10], the addition of a third cytotoxic drug [11]-[16] and, more recently, the combination with new agents. Overall, results have been disappointing even though the addition of gemtuzumab ozogamycin (GO), an antiCD33 monoclonal antibody conjugated with the cytotoxic agents chaliceamycin, has been reported to confer a significant advantage in selected patients with AML [17]-[21]. Notwithstanding, in absence of intensive post-induction therapy virtually all patients will ultimately relapse, therefore consolidation therapy is strictly needed. At present, after CR achievement all patients receive a consolidation chemotherapy based on intermediate or high dose ARA-C and then in young adult patients three options can be considered, i.e. allogeneic stem cell transplantation (allo-SCT), autologous SCT (ASCT) or repetitive intensive consolidation chemotherapy cycles (ICC) with high or intermediate dose ARA-C [22]-[37], depending on age, disease risk and donor availability. In particular, it is widely accepted that ICC and ASCT would be limited to patients with favorable risk, such as AML with t(8;21), AML with inv(16) or t(16;16) and AML with normal karyotype with NPM1 mutation in absence of mu-

tations of FLT3/ITD gene [38], [39]. In the remaining patient population, allo-SCT must be considered when age and performance status result in an acceptable risk/benefit ratio. In this regard, it should be considered that in the last years morbidity and mortality from allo-SCT have been considerably reduced; in addition, the introduction into daily practice of reduced intensity conditioning (RIC) has allowed to offer the procedure to selected old and/or previously not eligible patient population.

Currently, even in patients with favourable prognostic factors at diagnosis, the role of ASCT remains unclear although most studies that have compared ASCT with ICC demonstrated a significantly lower rate of relapse following ASCT (5,6). Results in terms of survival were, however, less encouraging because of transplant-related deaths and the low rate of second CR in patients who relapsed after ASCT, therefore in the last year ASCT has become less popular, mainly in USA. Notwithstanding, different considerations should be made: first, both the occurrence of toxicity and mortality related to ASCT have greatly decreased since use of peripheral-blood stem cells was introduced, even in older patients. Second, reduction of relapse rate would represent a main therapeutic objective in the therapy of AML, just as it is any malignant disorder. Finally, consolidation therapy based on repeated courses of high-dose or intermediate-dose cytarabine is probably more toxic and costly than ASCT and is poorly feasible in patients aged over 55-60 years. In elderly patients, particularly, the dose intensification by either ASCT or ICC has failed so far to induce a significant benefit [40]-[42]. Therefore, novel more rational targeted agents are particularly warranted in this setting. On the other hand, two important conditions are necessary in order to perform ASCT: CR achievement and collection of an adequate number of CD34⁺ cells ($> 2 \times 10^6/\text{Kg}$). As the latter aspect is concerned, it should be mentioned that a previous history of myeloid disorder (especially myelodysplastic syndrome), advanced age and the use of certain drugs during the induction and consolidation phases (e.g. fludarabine [43]) can significantly impair the possibility to collect an adequate number of cells.

Overall, data from the literature are controversial, but it has been definitively demonstrated that ASCT provides better results in patients with favorable risk diseases and low amount of minimal residual disease after induction/consolidation therapy. In the last years, a few complete meta-analyses and extensive reviews tried to draw some conclusions but were not able to indicate definite guidelines [44]-[46].

In this chapter, the authors review the current knowledge on the use of SCT in post-consolidation therapy of AML, based on their own experience and the most recent literature data, by mainly focusing on randomized clinical trials (RCT).

2. Randomized clinical trials comparing autologous stem cell transplantation and chemotherapy or no further therapy

In 1995 Zittoun et al. for the EORTC-GIMEMA groups reported on 941 AML patients treated with one or two cycles of standard Daunorubicine/Cytarabine schedule (3/7). Patients obtaining CR were submitted to one consolidation cycle including high-dose cytar-

abine (HD-AC) and Amsacrine. Subsequently, patients with HLA identical donor were allo-transplanted, whereas patients without HLA identical donor were randomized to receive ASCT or a second consolidation (ICC) with daunorubicine and HD-AC. The CR rate after induction therapy was 66%. The relapse rate were 40% in the two arms (ASCT) and 57% (ICC), respectively; DFS was longer for patients submitted to ASCT compared to patients submitted to ICC (48% vs 30%; $p=0.05$). However the OS was not significantly superior in the ASCT group, due to the greater ability of ASCT to rescue relapsed patients in the ICC arm [24].

In 1997 Harousseau and Colleagues reported data on 517 eligible patients (15-50 years of age) affected by previously untreated AML. Patients received 3 - 4 courses of conventional induction treatment (Ara-C: 200 mg/sqm/day for 7 consecutive days with either idarubicin administered intravenously on days 1 - 5 at a daily dose of 8 mg/sqm or rubidazole administered intravenously on days 1 - 4 at a daily dose of 200 mg/sqm). Patients aged 40 year or younger, in CR after induction therapy, were assigned to SCT if an HLA identical donor was available. All other patients received a first course of HD-Ara-C (3 gr/sqm) administered every 12 hours along 4 days (ICC) and then were randomized to receive either a second course of ICC or an ASCT. Eighty-eight patients out of 517 received an SCT, while 164 out of 517 were eligible for randomization (75 received ASCT, 71 received ICC). No differences in terms of OS and DFS were observed between the two arms: the 4 years DFS was 44 +/- 5.5% in ASCT group and 40.5 +/- 5.5% in ICC group (p value 0.41); the 4 years OS was 50 +/- 6% in ASCT group and 54.5 +/- 6% in ICC group (p value 0.72). The retrospective analysis of DFS and OS based on the cytogenetic risk could not detect any differences between the ASCT group and the ICC group [28].

In 1998 Cassileth et al. reported on 740 AML patients treated with standard 3/7 - 3/5 induction - consolidation chemotherapy cycles. Patients without an HLA identical donor were randomized between ASCT and HD-AC. The overall CR rate was 70%; the 4-years-DFS was 35% in both groups; the 4 years OS was 43% in ASCT group and 52% in ICC group respectively ($p=0.05$) [25].

The first report on the MRC AML 10 trial was published in 1998 [29]. Patients were firstly randomly assigned to different induction chemotherapy regimens (DAT vs. ADE); all patients achieving CR after two induction courses received a third consolidation chemotherapy course (MACE). Patients who lacked an HLA-matched sibling donor were randomized to receive one more chemotherapy course (MidAC) followed by either ASCT or no further therapy; patients with an HLA-matched sibling donor were assigned to receive an SCT. Basis on the intention to treat analysis the number of relapses was significantly lower in the ASCT group than in the group assigned no further treatment (37% vs. 58%; $p=0.0007$), resulting in superior DFS at 7 years (53% vs. 40%; $p=0.04$). No difference in terms of OS was observed. Of note, however, in this trial only 38% of patients available for randomization were randomized [29].

Tsimberidou et al. then reported data on 120 patients with de novo AML in 2003. All patients were treated with standard 3/7 regimen (2 courses) and if in CR underwent a first HD-AC course. All patients aged less than 50 years and with an HLA compatible donor received

an SCT; patient aged more than 50 years or without an HLA-matched sibling donor were randomly assigned to receive a second HD-Ara course or an ASCT. With a median follow-up of 43 months the 3-year failure free survival rates was 42% for patients receiving ASCT and 33% for patients receiving conventional chemotherapy [33].

Subsequently, Breems et al in 2005 reported data on 646 patients enrolled in the HOVO/SAKK AML4 trial. After two cycle of induction therapy combining cytarabine with daunorubicine (first course) and amsacrine (second course), CR patients (75%) were addressed to a consolidation therapy with mitoxantrone and VP16. Eighty-one patients received SCT. Patients non eligible for SCT were randomized between ASCT (66 patients) and no further therapy (46 patients). After a median follow up of 154 months, there were no statistically significant differences concerning DFS, OS and relapse rate within the two randomization arms. There was a trend towards a better OS of the non-autografted patients. This was associated with a higher, though non significant, incidence of death in CR within the auto-transplanted group with respect to the no treatment group. The 5 years OS after relapse for patients previously auto-grafted was significantly shorter with respect to patients who received no further treatment [34].

A large European intergroup trial [47] later evaluated HD-AC induction and escalation of post-remission therapy in a 2-stage RCT. Patients under the age of 60 years were randomized to 1 of 2 induction courses (double HD-AC vs. standard cytarabine/HD-AC). Patients in remission received a third cycle of chemotherapy followed by a second randomization to ASCT or maintenance chemotherapy. Fifty-one percent assigned to maintenance received the assigned therapy, while only 24% received the assigned ASCT. Three-year remission duration was 50% versus 44%, 3-year relapse-free survival was 48% versus 43% for maintenance and ASCT, respectively, and there was no significant difference between the 2 arms when stratified according to cytogenetic risk profile [47].

An update of the AML10 study was then reported in 2006 [35]. Briefly, The overall survival of patients allocated to autologous transplantation was better than for those in the no-further-therapy arm (53% vs. 45%) at 10 years, with 165 patients at risk at that time point. Of note, although this difference was not statistically significant on a log-rank analysis ($P=.09$), the Kaplan-Meier plots clearly diverged after the first 3 years, the difference becoming significant. This was related to a highly significant reduction in relapse risk in the autograft arm (40% vs. 58%; $P=.0005$), with consequent improved DFS in the ASCT arm (50% vs. 39%; $P=.03$), a data which was partially obscured by a higher risk of death in remission (16% vs. 6%; $P=.02$). Overall, the study suggested a survival benefit with ASCT in patients in the good- and standard-risk groups but not in the poor-risk group. Conversely, it was unclear if any specific age group benefited [35].

Based on these studies, a couple of systematic meta-analyses and reviews, tried to delineate some possible indications. However, many data were conflicting a definitive recommendations appeared difficult. Particularly, Nathan and Colleagues performed a comprehensive meta-analysis on consolidation therapy for AML. In particular, they analyzed 6 studies including 1044 patients randomly assigned to receive ASCT vs. ICC (5 studies), or ASCT vs. no further treatment (1 study). Patients receiving ASCT had a better disease free but not differ-

ent overall survival. Thus, they did not recommend ASCT as routine options for AML patients in first CR [45]. Thereafter, Visani and Colleagues, based on evidence based medicine (EBM) criteria, considered 6 RCT evaluating the role of ASCT and concluded that due to the heterogeneity of AML biology (i.e. molecular genetics), further studies specifically dedicated to the different entities were probably necessary to build robust recommendation according to EBM rules [46].

More recently, the HOVON Group reported the results of a prospective, randomized phase 3 trial evaluating ASCT vs. ICC in newly diagnosed AML patients in first CR (CR1) [48]. Patients with AML (16-60 years) in CR1 after 2 cycles of intensive chemotherapy and not eligible for allogeneic SCT were randomized between ICC (including etoposide and mitoxantrone) or ASCT (Bu/Cy). More than 90% of randomized patients received their assigned treatment (ICC, n = 259; ASCT, n = 258). The 2 groups were comparable with regard to prognostic factors. The ASCT group showed a markedly reduced relapse rate (58% vs. 70%, $P = 0.02$) and better relapse-free survival at 5 years (38% vs. 29%, $P = 0.065$) with non-relapse mortality of 4% vs. 1% in the chemotherapy arm ($P = 0.02$). OS was similar (44% vs. 41% at 5 years, $P = 0.86$), possibly because of more opportunities for salvage with second-line chemotherapy and SCT in patients relapsing on the chemotherapy arm. [48].

Finally, Pflman et al reported the results of the AML96 trial [49], aiming to differentiate groups of patients according to the treatments that would provide them optimum benefit. Five hundred eighty six AML patients (aged below 60 years) - excluding those with t(8;21) - in CR1 after double induction treatment were consolidated with SCT or ASCT, or ICC containing HD-AC, in a priority-based and risk-adapted manner. The association between potentially prognostic variables and OS was assessed and a post-remission treatment (PRT) score was developed in 452 patients with a complete dataset. This score was then validated in additional 407 patients from the AML2003 trial. Age, percentage of CD34-positive blasts, FLT3-ITD mutant-to-wild-type ratio, cytogenetic risk, and de-novo or secondary AML were identified as independent prognostic factors, and included in the PRT score. Accordingly, patients were separated into three groups: favorable (N=190; 3-year survival 68%), intermediate (N=198; 49%), and unfavorable (n=64; 20%). These results were confirmed in the AML2003 trial dataset: 3-year survival for the favorable group (n=265) was 69%, for the intermediate group (n=114) it was 61%, and for the unfavorable group (n=28) it was 46%. Therefore, the 3 groups presented with significantly different survival probabilities ($p=0.015$). Additionally, the Authors found that in the favorable group, patients who received SCT (n=60) had higher survival probabilities (82%) than did those given chemotherapy (n=56, 55%; $p=0.0012$) or ASCT (n=74, 66%; $p=0.044$). In the intermediate PRT score group, patients receiving ASCT (n=69) had the best survival probabilities (62%) compared with those given chemotherapy (n=72, 41%; $p=0.0006$) or SCT (n=57, 44%; $p=0.0045$).

Overall, the study thus supported the use of autologous HSCT in patients aged 60 years or younger with an intermediate PRT score.

Results of the above mentioned studies on ASCT are summarized in Table 1.

Author	Population – Study design	Outcome		Pvalues
		Auto-SCT	Chemotherapy/no further therapy	
Zittoun et al	990 patients (< 59 y) previously untreated AML. (941 evaluable)	4 yrs DFS: 48 ± 5%	4 yrs DFS: 30 ± 5%	0.05
	Study design:	4 yrs OS : 56 ± 5%	4 yrs OS : 56 ± 5%	NS
	- Induction: cytarabine + doxorubicine			
	If PR: 2 nd course of induction therapy			
	Consolidation: HDAC+amsacrine			
	If CR, age<45 yrs and HLA compatible donor: allo-SCT (N= 144)			
Harousseau et al	- If > 45 yrs and/or no HLA compatible donor: randomization (auto-SCT, N= 95 vs. 2 nd course of intensive therapy, N=104)			
	517 previously untreated AML patients (15-50 yrs)	4 yrs DFS: 44 ± 5.5%	4 y DFS: 40.5 ± 5.5%	NS
	Study design:	4 yrs OS: 50 ± 6%	4 y OS: 54.5 ± 6%	
	- Induction: cytarabine and idarubicine or rubidazone. If no CR: 2 nd cycle		Low risk group	
	- Consolidation: HD-AC + Idarubicine or Rubidazone	4 yrs DFS: 50 ± 9%	4 yrs DFS : 56 ± 11%	NS
	If CR, age <40 yrs and HLA compatible donor: allo-SCT (N=88)	4 yrs OS: 59 ± 9%	4 yrs OS: 71 ± 8%	NS
	- If > 40 yrs and/or no HLA compatible donor: randomization (auto-SCT, N= 75 vs. ICC, N=71)			
			Intermediate risk group	
		- 4 yrs DFS: 38.5 ± 9%	- 4 yrs DFS: 31 ± 8.5%	NS
		- 4 yrs OS: 42.5 ± 9%	- 4 yrs OS: 55 ± 9%	NS
Cassileth et al			High risk group	
		- 4 yrs DFS: 38 ± 10%	- 4 yrs DFS: 28.5 ± 10%	NS
		- 4 yrs OS: 46.5 ± 11%	- 4 yrs OS: 40 ± 11.5%	NS
	772 previously untreated AML patients (16-55 yrs)	4 yrs DFS: 35±9 %	4 yrs DFS: 35±9 %	NS
	Study design:	4 yrs OS: 43±9 %	4 yrs OS: 52±9 %	P=0.05

Author	Population – Study design	Outcome		Pvalues
		Auto-SCT	Chemotherapy/no further therapy	
Burnett et al	Induction: 2 cycles of idarubicine and cytarabine Consolidation: idarubicine and cytarabine - If CR and HLA compatible donor: allo-SCT (N=113) - If not HLA compatible donor: randomization auto-SCT (N =116) vs. HD-Cytarabine (N = 117)			
	1509 previously untreated AML patients aged less than < 56 yrs <i>Study design:</i>	10 yrs DFS: 50%	10 yrs DFS: 39%	0.03
	- 2 Induction: Daunorubicine, Cytarabine, Thio-guanine vs Daunorubicine, Cytarabine, VP-16	10 yrs OS: 53%	10 yrs OS : 45%	0.009
	- 1 st Consolidation: Amsacrine, Cytarabine, VP-16			
	- Pts with HLA identical donor: 2 nd consolidation (Mitoxantrone, Cytarabine) and allo-SCT - Pts lacking HLA identical donor: 2 nd consolidation (Mitoxantrone, Cytarabine) and randomization to auto-SCT (N =190) vs. no further therapy (N =191)	Relapse rate at 10 yrs: 40%	Relapse rate at 10 yrs: 58%	0.0005
Tsimberidou et al	120 previously untreated AML patients (<60 yrs) <i>Study design:</i>	3 yrs OS: 58%	3 yrs OS: 46%	NS
	- 2 Induction: Idarubicine, Cytarabine (3+7) - Consolidation: HD-AC	3 yrs FFS: 42%	3 yrs FFS: 33%	NS
	- If < 50 y and HLA compatible donor : allo-SCT (N = 21)			
	- If > 50 y and/or no HLA compatible donor: randomization (auto-SCT, N = 19 vs. 2 nd HD-AC, N= 15)			
Breems et al	646 previously untreated AML patients (< 60 years) <i>Study design:</i>	5 yrs DFS: about 35%	5 yrs DFS: about 37%	NS
	- Induction 1: Daunorubicine, Cytarabine (3+7)	5 yrs OS : about 45%	5 yrs OS : about 55%	NS

Author	Population – Study design	Outcome		Pvalues
		Auto-SCT	Chemotherapy/no further therapy	
	- Induction 2: Amsacrine, Cytarabine	7 pts died in CR within 9 months	1 pts died in CR within 9 months	NS
	- Consolidation: Mitoxantrone, VP16			
	- If eligible and compatible donor : allo-SCT (N = 81)	5 yrs OS after re-lapse: about 5%	5 yrs OS after re-lapse: about 25%	0.003
	- If non eligible: randomization (auto-SCT, N =66 vs. no therapy, N = 64)			
Buchner et al.	840 AML/high-risk MDS patients (age ≤ 60 years)	3 yrs DFS: 48%	3 yrs DFS: 46%	0.65
	Study design:			
	1st Randomization at induction: TAM-HAM vs. HAM-HAM	3 yrs OS : 43%	3 yrs OS : 41%	0.52
	TAD: thioguanine, cytarabine, and daunorubicin			
	HAM: cytarabine and mitoxantrone			
	Consolidation: TAD			
Vellenga 2011	2nd Randomization (auto-SCT, N=429 vs. maintenance, N = 411)			
	If eligible and compatible donor : allo-SCT (N= 128)			
	2,017 AML patients (age ≤ 60 years)			
Vellenga 2011	Induction 1: cytarabine and idarubicinInduction 2: cytarabine and amsacrine	5 yrs DFS: 38%	5 yrs DFS: 29%	0.065
	Consolidation: etoposide and mitoxantrone	5 yrs OS: 44%	5 yrs OS : 41%	0.86
	Randomization to ASCT (N=258) vs. Chemotherapy (N=259)	Relapse rate: 58%	Relapse rate: 70%	0.02
Pfirman 2012	1,151 AML patients (age ≤ 60 years)	Favorable PRT:		
	Assignment to ASCT (N=191) vs. Chemotherapy (N=223)	3 yrs OS: 66%	3 yrs OS : 55%	
	Assignment to SCT (N=172)	Intermediate PRT:		
		3 yrs OS: 62%	3 yrs OS : 41%	0.0006
		Adverse PRT:		
		3 yrs OS: 7%	3 yrs OS : 19%	

Table 1. Summary of the most relevant randomized clinical trials evaluating the role of ASCT in AML

3. Discussion and perspectives

Current intensive induction chemotherapy for patients with AML produces CR rates higher than 60-65 %; however, less than 30% of patients still survive for more 5 years free of disease. In this context, the aim of post-remission treatment is to eradicate clonogenic leukemic cells, which persists after induction and are ultimately able to induce disease relapse. Nonetheless, the optimal form of treatment is still under debate. As discussed, three main strategies are used to prevent relapse in patients with AML in first CR, including intensive chemotherapy based on intermediate-dose or high-dose cytarabine, and allogeneic and autologous hemopoietic stem cell transplantation. The choice among these approaches for an individual patient relies on two main factors, namely the expected risk of relapse as determined by biological features of leukemic cells and expected morbidity and mortality associated with a specific option, according to age and comorbidities [50].

Intensive chemotherapy (ICC) proved to be useful for improving AML patients outcome [17], [19]-[21], [51]-[55].

On the other hand, allogeneic SCT was demonstrated to be the most effective strategy to reduce the relapse risk [24], [25], [28], [29]. However, it is associated with a high-risk of treatment-related morbidity and mortality (TRM), and it is conventionally offered to younger patients with a HLA-matched sibling or unrelated donor. Of note, in the last years several evidences emerged that allogeneic SCT should not be offered as first option to patients with relatively favorable biological characteristics. The latter include a few genetic abnormalities – $t(8;21)(q23;q22)$, $inv(16)(p13q22)$, and $t(15;17)(q22;q21)$ – as well as the presence of somatic mutations of *NMP1* and/or *CEBPA* genes in absence of other abnormalities. Therefore, for these patients, with the exception of M3 patients that can benefit from specific targeted agents, once achieved CR, the most suitable therapeutic options remain intensive chemotherapy and ASCT.

ASCT is an alternative approach to deliver an effective anti-leukemic myeloablative therapy to AML patients in CR, when a donor is not available. It has been demonstrated that ASCT is feasible and effective in AML, provided that an adequate induction/consolidation treatment has previously determined an effective *in vivo* purging. In fact, the results obtained with ASCT can be significantly affected by other relevant factors, including intensity of induction and consolidation chemotherapy as well as conditioning regimens, which strongly influencing the MRD burden before the procedure is performed [50]. Bearing this in mind, it is not surprising that the several RCT trying to define the role of ASCT as post-remission therapy in AML ended up with discrepant result. In particular, the nine largest studies, though considering 2,894 patients assigned to either ASCT or chemotherapy/no further therapy (among more than 8,000 enrolled ones) did not reach definitive conclusions (Table 1). In fact, although a reduced relapse risk was often recorded, only one study provided evidences of survival advantages for patients receiving ASCT, considering the whole population [35], while one assessed a significant advantage only in

patients with an intermediate prognostic score [49]. Indeed, in most instances, the reduced leukemia recurrence was balanced by an increase TRM. In this regard, however, it should be mentioned that in the last years the mortality of ASCT has definitely declined, possibly challenging some of the results published so far. Moreover, reduction of the relapse rate is a pivotal objective in the treatment of AML, as the only way toward the cure. In addition, the continuous and very fast improvement in our knowledge of the biology of the disease on one hand clearly established that AML is not a unique disease, providing the basis for future more rationale therapies based on the specific molecular features, while on the other hand made more difficult to be interpreted results from most clinical trials, that were initiated when a comprehensive molecular characterization was not available. Accordingly, a modern view of the problem should consider these new elements and rather than debating whether ASCT is superior to SCT or ICC in AML, it would be more useful to identify those patients who would more benefit from the procedure.

Of note, one study (actually the most recently published) tried to identify the optimal post-remission strategy according to both clinical and biological features of the single case, recognizing three different groups based on an original post-remission treatment (PRT) score. Indeed, ASCT turned out to be the treatment of choice for the intermediate class, the outcome being quite favourable (Table 1). Therefore, although the proposed scoring systems will be probably modified/updated in the future, following, for example, the knowledge derived from the most recent massive parallel sequencing studies [56] and the introduction of novel anti-leukemic compounds, an interesting scenario has probably (re)opened for ASCT. Finally, future research should focus on designing better ways to do autografts rather than conducting more trials comparing chemotherapy with the same autograft procedures currently in use, including the adoption of immunotherapy, the selection of patients based on the absence of a minimal residual disease [57] and/or of new biologic molecularly targeted compounds in the post-ASCT phase.

In conclusion, although evidence based indication cannot be offered for ASCT in AML, it is reasonable to consider it as a valid therapeutic option for AML patients at low-intermediate risk in CR1. Indeed, a main goal should be having optimal frontline genetic characterization, as well as MRD evaluation on the harvested cells. For high risk patients, unfortunately, SCT can be an option, if they achieve a good quality CR; otherwise, experimental procedures are mandatory.

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