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Autologous Hematopoietic Stem Cell Transplantation in Acute Myelogenous Leukemia

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The clinical outcomes of autologous hematopoietic stem cell transplantation (ASCT) in acute myelogenous leukemia (AML) have improved over time. Indeed, numerous studies have demonstrated that ASCT is associated with a lower relapse rate and acceptable nonrelapse mortality compared with chemotherapy alone in patients with AML. In addition, ASCT is also associated with comparable overall survival outcomes to those of allogeneic hematopoietic stem cell transplantation in some patients with AML. To date, age, cytogenetic and molecular risk stratification, and minimal residual disease (MRD) status have been shown to be closely related to clinical outcomes following ASCT. ASCT is recommended for patients with favorable-risk and intermediate-risk AML in first complete remission and patients with acute promyelocytic leukemia in second complete remission for whom a matched sibling donor is not available. MRD status pre-ASCT is the most important factor to consider when determining whether a patient is eligible for ASCT and can effectively predict clinical outcomes after ASCT. Advanced age is not an absolute contradiction for ASCT. In this review, we describe the literature and clinical trials evaluating the outcomes of ASCT in patients with AML and discuss the indications for ASCT therapy. Because the greatest concern in ASCT recipients is early relapse, important factors that should be monitored before ASCT and future perspectives in this area are also presented.

INTRODUCTION

With the development of allogeneic hematopoietic stem cell transplantation (allo-SCT) from alternative donor sources, including unrelated donors, umbilical cord blood, and haploidentical transplantation (haploSCT), the clinical application of autologous hematopoietic SCT (ASCT) has decreased [1]. The clinical outcomes associated with ASCT have improved over time, however. European researchers retrospectively analyzed the survival outcomes in 809 ASCT recipients with acute myelogenous leukemia (AML) in first complete remission (CR1) and found 2-year leukemia-free survival (LFS) and overall survival (OS) rates as high as 51% and 65%, respectively [2], with a nonrelapse mortality (NRM) of only 3.7% [3]. In addition, Simancikova et al [4] evaluated long-term survival in patients who underwent ASCT with AML in CR1 and found a 5-year OS of 60.8%.

ASCT remains an important postremission therapy for patients with AML. Accordingly, in this review, we focus on the clinical outcomes of ASCT in patients with AML and discuss the main prognostic factors predictive of ASCT efficacy based on data from the literature and clinical trials. We aim to provide insight into decision making regarding the optimal use of ASCT in patients with AML.

ASCT VERSUS CHEMOTHERAPY

Although standard intensive chemotherapy may induce morphological CR for AML, relapse is a common cause of poor long-term survival outcomes. Because it provides significant antileukemia effects with a low NRM while avoiding the risk of graft-versus-host disease (GVHD) associated with allo-SCT, ASCT is an alternative postremission therapy in selected patients with AML. ASCT also has the advantage of a lower relapse risk (RR) than chemotherapy alone in patients with AML, particularly those with good- or intermediate-risk molecular cytogenetics [5–7]. To assess the value of ASCT in AML, Burnett et al [8] prospectively compared the clinical outcomes of 381 patients age <56 years in CR1 who had received 4 courses of intensive chemotherapy and showed that ASCT was associated with significantly lower RR in patients in all risk groups compared with patients who did not undergo ASCT, leading to an improvement in 7-year LFS (53% versus 40%; $P = .04$). In another study of patients with AML in CR1 age >65

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years, both progression-free survival (PFS) and OS were significantly better in patients who underwent ASCT compared with those who did not [7].

Cornelissen et al [5] retrospectively compared outcomes after ASCT (n = 152) and chemotherapy (n = 271) in patients with AML in CR1 and found better 5-year OS (54 ± 3% versus 40 ± 3%; $P = .02$) and LFS (44% versus 30%; $P < .001$), with no significant difference in NRM, following ASCT. In a prospective, randomized phase 3 trial, patients with AML with CR1 status not eligible for allo-SCT were randomly assigned to receive ASCT following a high-dose cyclophosphamide and busulfan (BuCy) conditioning regimen (n = 258) or intensive chemotherapy with etoposide and mitoxantrone (n = 259). The results showed that ASCT was associated with lower 5-year RR (58% versus 70%; $P = .02$); however, OS was comparable in the 2 arms, possibly because more relapsed patients in the chemotherapy arm received life-saving treatment, such as second-line chemotherapy and transplantation [6]. An early prospective trial that focused on survival outcomes following 3 types of postremission therapy in patients with AML in CR1 demonstrated better LFS with ASCT and allo-SCT compared with intensive chemotherapy. The 4-year LFS was 55% in recipients of matched sibling donor (MSD)-allo-SCT, 48% in recipients of ASCT, and 30% in recipients of chemotherapy, and ASCT was associated with a superior LFS compared with chemotherapy alone (RR = .73; $P = .05$) [9]. In another study, in patients with AML in the favorable risk group and in CR1, the 5-year LFS was better after ASCT than after chemotherapy alone (60% versus 32%) [10].

Overall, these findings suggest that ASCT is safe, with acceptable transplantation-related toxicity, in patients with AML and is associated with lower RR and better LFS than chemotherapy alone. However, these data were obtained mainly from retrospective studies. Therefore, additional prospective studies are urgently needed to determine whether ASCT will lead to improved OS rates in these patients, particularly with the significantly reduced NRM.

ASCT VERSUS ALLO-SCT

SCT, including ASCT and allo-SCT from MSDs or matched unrelated donors (MUDs), is an important postremission therapy for AML. MSD-allo-SCT remains the best choice for patients with AML considering transplantation [11]; however, ASCT can yield OS rates comparable to those of MSD-allo-SCT in some patients, and ASCT is associated with comparable or better survival outcomes when using unrelated donors or familial-mismatched donors, particularly in intermediate-risk patients [5,12–18]. ASCT and allo-SCT in patients with AML are compared in Table 1. In 2 prospective HOVON-SAKK phase III trials, comparable OS was observed in patients with intermediate-risk AML following ASCT and allo-SCT in CR1 [5]. In a retrospective study of 172 patients with AML in CR1, OS and disease-free survival (DFS) did not differ significantly between patients who underwent ASCT and those who underwent MSD-allo-SCT [18]. Mizutani et al [12] evaluated survival outcomes after autologous peripheral blood stem cell transplantation (n = 357) and MSD-allo-SCT from bone marrow (n = 521) or peripheral blood (n = 380) in patients with AML in CR1 and found that although RR after ASCT was relatively higher, NRM was significantly lower compared with MSD-allo-SCT, and LFS did not differ significantly in multivariate analyses. Comparable LFS and OS at 5 years were also observed in another study comparing MSD-allo-SCT and ASCT [13]. Yoon et al [19] suggested that ASCT should be considered for selected patients with intermediate-risk AML in CR1 after standard

Table 1
ASCT versus Allo-SCT in Patients with AML

Reference	Study Type	Patients	Comparison	OS	DFS	NRM	RR
Cornelissen et al [5]	Prospective	Intermediate-risk, CR1	Allo-SCT (n = 161) vs ASCT (n = 93)	60 ± 4% vs 54 ± 5%; $P > .05$			
Zittoun et al [9]	Prospective	CR1	MSD-allo-SCT (n = 168) vs ASCT (n = 128) vs CT (n = 126)		4-year DFS: 55% vs 48% vs 30%		
Yao et al [18]	Retrospective	CR1	ASCT (n = 46) vs MSD-allo-SCT (n = 126)	73.6% vs 74.6%; $P = .616$	69.1% vs 73.6%; $P = .559$	4.3% vs 11.2%; $P = .215$	26.6% vs 14.1%; $P = .083$
Keating et al [13]	Retrospective	CR1	MSD-allo-SCT vs ASCT	61% vs 54%; $P = .19$	58% vs 47%; $P = .13$		
Mizutani et al [20]	Retrospective	CR1	APBSCT (n = 177) vs MUD-BMT (n = 173)	66% vs 64%; $P = .83$	64% vs 58%; $P = .16$	7% vs 17%; $P = .005$	
Gorin et al [3]	Retrospective	CR1	ASCT (n = 373) vs MUD-allo-SCT (n = 335)	83% vs 62%; $P = .008$	67% vs 64%; $P > .05$	3.7% vs 19%; $P < .0001$	29% vs 17%; $P < .0001$
Chevallier et al [17]	Retrospective	CR2	ASCT(n=82)vsCBT(n=99)	59 ± 6% vs 50 ± 6%; $P = .45$	57 ± 6% vs 46 ± 6%; $P = .37$		
Gorin et al [15]	Retrospective	CR1/CR2	ASCT (n = 253) vs haploSCT (n = 132)	64% vs 57%; $P = .12$	47% vs 48%; $P = .73$	4% vs 25%; $P < .00001$	50% vs 27%; $P < .00001$
Chen et al [16]	Retrospective	CR1	ASCT (n = 88) vs haploSCT (n = 107)	79.0% ± 4.6% vs 80.1% ± 5.0%; $P = .769$	66.1% ± 5.2% vs 77.4% ± 4.8%; $P = .079$		

CT indicates chemotherapy; APBSCT, autologous peripheral blood SCT; BMT, bone marrow transplantation; CBT, cord blood allo-SCT.

chemotherapy; in multivariate analysis, the 5-year DFS after ASCT did not differ significantly between this subgroup of patients and recipients of MSD- or MUD-allo-SCT, and ASCT was associated with lower NRM. Therefore, ASCT can be considered an effective postremission therapy for patients with AML in CR1 who cannot undergo MSD-allo-SCT.

In a comparison between ASCT and allo-SCT from unrelated donors, Gorin et al [3] showed that ASCT was associated with a lower NRM and better OS in patients with AML in CR1. Saraceni et al [14] retrospectively evaluated patients with AML in CR1 who underwent allo-SCT from 10/10 MUDs (MUD-SCT), allo-SCT from unrelated donors with a mismatch at a single HLA locus (9/10 UD-SCT), and ASCT, and found that ASCT yielded OS rates comparable to those of MUD-SCT and 9/10 UD-SCT. Moreover, ASCT was associated with a significantly better OS compared with 9/10 UD-SCT in intermediate-risk patients. Another study comparing ASCT with MUD-allo-SCT in cytogenetically normal patients with AML in CR1 found lower NRM in the ASCT recipients, but comparable LFS and OS in the 2 groups of patients [20].

Gorin et al [15] analyzed 544 patients with acute leukemia who received ASCT or allo-SCT, with a median follow-up of 28 months, and found no significant differences in LFS or OS for all patients with AML who received ASCT or T cell-replete haploSCT. Notably, in their study, ASCT was associated with a better OS in patients with intermediate-risk AML compared with haploSCT, but after removing transplantation centers that treated fewer than 5 patients per year, the difference disappeared. Similarly, Chen et al [16] reported equivalent survival outcomes after ASCT and haploSCT in patients with favorable- and intermediate-risk AML in CR1, with no significant differences in OS or RFS. In a comparison of ASCT and cord blood allo-SCT (CBT), multivariate analyses showed that the higher RR in autografted patients was compensated for by a lower NRM, resulting in comparable 3-year OS and LFS [17].

Overall, the published data suggest that ASCT may be an effective postremission therapy for favorable- and intermediate-risk patients with AML who are not eligible for MSD-allo-SCT.

PROGNOSTIC FACTORS FOR ASCT IN AML

Age

The typical cutoff age distinguishing patients with relatively favorable outcomes from those with poor LFS and OS is 50 years [2,21–27]. Eom et al [24] reported poor survival outcomes after ASCT in a subset of patients with AML age >50 years and harboring t(8;21). Saraceni et al [2] found that age >50 years was an independent prognosis factor for poor survival outcomes in patients with AML who underwent ASCT. Nagler et al [22] reported that in patients with AML in CR1, OS (77 ± 2% versus 56.3 ± 3%; $P < .001$), LFS (61 ± 3% versus 45 ± 3%; $P < .001$), and NRM (4 ± 1% versus 10 ± 2%; $P < .001$) were superior in those age <50 years compared with older patients, consistent with results of other studies [23,24,26]. In another study, the cutoff age for distinguishing OS and LFS following ASCT was 55 years [28].

Although most studies have identified age as an important prognostic factor for outcomes after ASCT, age had no impact on outcomes following ASCT in some studies [7,16,29]. In a single-center retrospective study of patients with AML in CR1 age ≥65 years, LFS and OS were 48.2% and 60.6%, respectively, and there were no significant differences in PFS and OS after ASCT between patients age ≥65 years and those age <65 years [7]. Recently, Mueller et al [30] retrospectively analyzed 148 consecutive patients with AML who underwent ASCT at the same center and found no differences in transplantation-related mortality (TRM), PFS, or OS according to age (age cohorts: <60 years, 60 to 64 years, and >64 years). These findings suggested that patients tolerate and benefit from ASCT equally, regardless of age. In a European single-center study [29], the 3-year DFS and OS after ASCT in elderly patients with AML were 60% and 68%, respectively, and TRM was only 3.4%. However, these outcomes were all obtained from retrospective studies, and the nonrandomized design inevitably led to selection bias. Age is an unreliable parameter; tolerance of induction treatment, performance status, and cytogenetic risk features also should be taken into consideration. The data demonstrate that ASCT is safe and effective in selected elderly patients with AML, and that although age is an adverse prognostic factor, it should not be viewed as an absolute contraindication for ASCT in AML.

Cytogenetic and Molecular Risk Stratification

Cytogenetic risk stratification is a crucial factor influencing clinical outcomes in patients with AML after ASCT. Patients with unfavorable-risk molecular cytogenetics have relatively higher RR and lower OS after ASCT compared with patients with favorable- to intermediate-risk molecular cytogenetics. Nagler et al [22] retrospectively analyzed outcomes in 952 patients with AML who underwent ASCT with a busulfan-based conditioning regimen. Multivariate analysis identified risk stratification as an important prognostic factor for both OS and LFS after ASCT. Yoon et al [21] reported similar outcomes in 240 patients with AML in CR1 who underwent ASCT following a conditioning regimen including total body irradiation (TBI; 1200 cGy), cytarabine (9 g/m^2), and melphalan (100 mg/m^2); OS decreased as the cytogenetic risk increased at 5 years after ASCT, with the highest 5-year OS in 19 patients carrying t(8;21) with isolated Y chromosome loss. In a previous study, we identified cytogenetic risk as an independent prognostic factor for survival outcomes, with decreasing OS and DFS as risk increased [18]. Gorin et al [3] compared ASCT with MUD-allo-SCT in patients with AML in CR1 and showed that favorable-risk patients benefited more from ASCT, intermediate-risk 2 patients had comparable outcomes after ASCT or MUD-allo-SCT, and intermediate-risk 1 patients had superior clinical outcomes after allo-SCT. Numerous other studies have also shown satisfactory outcomes after ASCT in patients with favorable- and intermediate-risk AML [5,12–17,25,31]. These studies support ASCT as a feasible treatment for patients with AML in CR1, particularly those with favorable- or intermediate-risk molecular cytogenetics.

Acute Promyelocytic Leukemia

The National Comprehensive Cancer Network guidelines indicate that ASCT should be considered for patients with acute promyelocytic leukemia (APL) in molecular CR2 after central nervous system prophylaxis [32]. In a phase 2 study of arsenic trioxide (ATO) followed by ASCT in patients with relapsed APL, Yanada et al [33,34] reported a 5-year event-free survival (EFS) of 65% and a 5-year OS of 77%, and concluded that ASCT was efficacious and feasible in patients with relapsed APL in CR2, particularly those who received ATO before ASCT, yielding higher 4-year LFS and OS than seen in patients who did not receive ATO.

In other studies, in patients with relapsed APL, OS was better after ASCT than after chemotherapy and ATO (Table 2) [35,36]. In a retrospective analysis of 155 patients (including 40 patients in molecular relapse, 104 in hematologic relapse, and 11 in extramedullary relapse after induction with ATO), of whom 93 underwent ASCT or allo-SCT after achieving CR2,

Table 2
ASCT in Relapsed APL

Reference	Disease Status	Comparison	EFS	OS	DFS	TRM	RR
Thirugnanam et al [37]	MR	ASCT (n = 14) vs ATO ± ATRA (n = 19)	5-yr EFS: 83.33% ± 15.21% vs 34.45% ± 11.24%; $P = .001$				
Ganzel et al [36]	CR2	ATO (n = 67) vs ASCT (n = 140)		5-year OS: 42% vs 78%; $P = .002$			
Holter Chakrabarty et al [38]	CR2	Allo-SCT (n = 232) vs ASCT (n = 62)		5-year OS: 54% vs 75%; $P = .002$	50% vs 63% $P = .10$;	31% vs 7% $P < .001$;	18% vs 30% $P = .40$;
de Botton et al [39]	CR2	Allo-SCT (n = 23) vs ASCT (n = 50)	7-yr EFS: 52.2% vs 60.6%; $P = .11$	51.8% vs 59.8% $P = .04$	92.3% vs 79.4%; $P = .19$	39% vs 6%	
		CT ± ATRA (n = 49)	30.4%	39.5%	38%		
Lengfelder et al [35]	CR2	ASCT (n = 60) vs allo-SCT (n = 33) vs CT or ATO ± ATRA (n = 55)		3-year OS: 77% vs 79% vs 59%; $P = .09$			3-year RR: 37% vs 39% vs 59%; $P = .05$

MR indicates molecular remission.

Lengfelder et al [35] found that ASCT and allo-SCT resulted in superior OS and LFS compared with additional cycles of ATO with or without all-trans retinoic acid (ATRA) or chemotherapy as consolidation treatment. In other studies of APL, ASCT was the preferred therapy for patients with CR2 status, and survival outcomes were superior in patients who received ASCT compared with those who received ATO-based consolidation therapy. Furthermore, OS was associated with the duration of CR1 ($P = .002$), but not with disease risk at diagnosis [36]. Thirugnanam et al [37] retrospectively compared different consolidation regimens in patients with relapsed APL who achieved molecular remission after an ATO-based induction regimen and showed that ASCT was associated with superior clinical outcomes (including 5-year EFS) compared with ATO-based regimens.

ASCT may be more effective than allo-SCT for treating patients with APL in CR2 [38,39]. Holter et al [38] compared ASCT with allo-SCT in patients with APL in CR2 for whom pretransplantation data on *PML-RARA* were available, and found that ASCT was associated with superior OS in both univariate and multivariate analyses. These results are consistent with the results of another retrospective analysis of patients with relapsed APL who were initially treated with ATRA and chemotherapy and then underwent ASCT or allo-SCT in CR2, in which OS was superior with ASCT and RFS and EFS did not differ significantly between the 2 treatments [39]. These data indicate that ASCT is an effective postremission therapy for patients with APL in CR2.

AML with t(8;21) or inv(16)

One study reported a 5-year OS of 88.8% following ASCT in patients with AML carrying t(8;21) with isolated Y chromosome loss [21], and comparable outcomes have been reported after ASCT and allo-SCT in patients with AML carrying t(8;21) [24,40,41]. Eom et al [24] reported an OS of 70.2% and a DFS of 68.4% at 5 years following ASCT in patients with AML with t(8;21) in CR1, and no significant differences in RR, OS, and DFS compared with patients who underwent allo-SCT with a reduced-intensity conditioning regimen. Similarly, in another study of patients with AML with inv(16) or t(8;21), ASCT was associated with a lower TRM compared with allo-SCT, and LFS was similar with the 2 treatments [40]. In addition, outcomes following ASCT were poorer in the patients with t(8;21) compared with those with inv(16), consistent with the results of other studies [42,43]. In a study reported by Qin et al [41], in patients with AML carrying inv(16), if *CBFB*/*MYH11* transcription levels decreased to .2% after 2 courses of consolidation therapy, then RR, DFS, and OS after ASCT were not significantly different from values in patients who underwent allo-SCT. Therefore, ASCT is a feasible treatment for patients with AML in CR1 carrying inv(16) or t(8;21).

AML with Double-Mutant CCAAT Enhancer Binding Protein Alpha (CEBPA) and AML with Mucleophosmin (NPM1)

Schlenk et al [10] compared ASCT and allo-SCT with chemotherapy in patients with AML in CR1 who harbored double-mutant *CEBPA* and showed better 5-year LFS with ASCT and allo-SCT compared with chemotherapy alone (60% versus 73% versus 32%). European researchers compared the clinical outcomes of ASCT in 19 patients with AML in CR1 harboring an isolated *NPM1* mutation (*NPM1*$^+$/*FLT3*$^-$) and another 80 patients with available data on both *NPM1* and *FLT3*/ITD mutations and showed that the patients with an isolated *NPM1* mutation were suitable for ASCT; after a median follow-up of 35 months, median OS and DFS were significantly improved [44]. Overall,

these findings suggest that ASCT is feasible for patients with AML in CR1 with favorable molecular cytogenetics.

AML with FLT3/ITD Mutation

FLT3/ITD mutation is a poor prognostic factor in patients with AML. Compared with chemotherapy, ASCT can improve survival outcomes in patients with *FLT3*/ITD mutation. In a systematic review and meta-analysis of published studies including 772 patients with AML in CR1 harboring an *FLT3*/ITD mutation, both allo-SCT and ASCT were associated with lower RR and better OS and DFS than chemotherapy alone, and there was no difference in OS and DFS between allo-SCT and ASCT [45]. An early study comparing the outcomes of 376 patients with AML according to *FLT3*/ITD mutation status found no significant difference in OS between patients who underwent ASCT and those who underwent allo-SCT in CR1; however, *FLT3*/ITD$^+$ patients in CR1 had a lower probability of survival following chemotherapy alone [46]. These results are consistent with those of another study in which patients with AML carrying an *FLT3* mutation who underwent ASCT showed similar 5-year OS and DFS, irrespective of *FLT3*/ITD mutation [47]. Of note, these studies may suggest better outcomes than actually occur, owing to the positive impact of the *NPM1* mutation and the low allelic ratio of *FLT3*/ITD.

In a study of the impact of *FLT3*/ITD and *NPM1* on the clinical outcomes of ASCT in 357 patients with cytogenetically normal AML, *FLT3*$^+$/*NPM1*$^-$ patients had the worst LFS and OS, whereas *FLT3*$^+$/*NPM1*$^+$patients who underwent ASCT in CR1 had 3-year OS and LFS rates comparable to those in *FLT3*$^-$/*NPM1*$^-$ patients [25]. With respect to the outcomes of different postremission therapies in patients with AML according to *NPM1*/*FLT3* molecular profile, data from a 2001 trial demonstrated that ASCT and allo-SCT yielded outcomes similar to those after chemotherapy alone in patients with an isolated *NPM1* mutation [48]. However, for the other patients, allo-SCT and ASCT yielded better 4-year LFS (68% versus 44% versus 36%) and OS (68% versus 52% versus 29%) compared with chemotherapy alone. Nevertheless, except in patients with an isolated *NPM1* mutation, no clear comparisons between patients with different *NPM1*/*FLT3* molecular profiles were reported [48]. Therefore, in patients with AML harboring an *FLT3*/ITD mutation in CR1, if an *NPM1* mutation were also present, ASCT could overcome the poor survival outcomes associated with *FLT3*/ITD.

In contrast, in a previous study, in patients with high-risk AML undergoing ASCT in CR1 with a busulfan and melphalan (BuMel) conditioning regimen, LFS was 53% at 2 years and 42% at 5 years [27], consistent with a study in which autografted CR1 patients, even those with high-risk AML, showed high 8-year DFS and OS (56% and 62%, respectively) [28]. Therefore, further studies are needed to determine whether CR1 patients with high-risk AML should be excluded from ASCT.

Overall, most studies published to date indicate that ASCT is associated with higher RR but lower TRM compared with allo-SCT. Given these results, ASCT may be a valid treatment for patients with favorable- to intermediate-risk AML in CR1 and for patients with APL in CR2, particularly when an HLA-identical sibling is not available. Impressive survival outcomes have been observed in patients with AML and unfavorable molecular cytogenetics after ASCT; however, the status of ASCT in high-risk patients should be confirmed in further studies.

Patients Autografted in CR1/CR2

Most studies reported to date have suggested superior clinical outcomes in patients autografted in CR1. In previous studies, the OS and DFS for patients with AML autografted in CR2 were poorer than those of patients autografted in CR1 [49]. Mollee et al [50] found differing survival outcomes in patients who autografted in CR1 and those who autografted in CR2, with higher 8-year EFS and OS in patients who autografted in CR1. However, Helbig et al [26] recently reported no differences between patients who autografted in CR1 and those who did so in CR2. Similarly, Nagler et al [22] found no differences in survival outcomes between patients with AML autografted in CR1 or in CR2 on univariate and multivariate analyses. Data for patients autografted in CR2 are limited, however, and based on available clinical outcomes, ASCT is mainly recommended for patients in CR1.

Minimal residual disease Status Pre-ASCT

The high rate of leukemia recurrence is a major concern in patients with AML who undergo ASCT, and recurrence of leukemia is the most common cause of mortality in these patients. Therefore, identification of strategies to decrease leukemia recurrence after ASCT is essential for improving outcomes of ASCT. Minimal residual disease (MRD) detection in patients and leukapheresis products pre-ASCT can be used to help select candidates for ASCT.

MRD is a crucial factor for distinguishing whether a patient with AML is eligible for ASCT. Real-time quantitative PCR (qPCR) and multiparameter flow cytometry (MFC) are effective techniques for monitoring MRD before and after ASCT in patients with AML [16,21,23,41,51–54]. MRD status pre-ASCT is an independent prognostic factor for both OS and RFS after ASCT [16]. Moreover, MRD status in patients and leukapheresis products at ASCT is closely related to RR and LFS [23]. Maurillo et al [51] evaluated MRD by MFC in patients with AML before ASCT and found that among 28 patients with positive MRD pre-ASCT, 23 relapsed; 5-year LFS and OS were only 14% and 28%, respectively, compared with 55% and 58% in patients with no detectable MRD. In addition, high MRD values (>.1% of the white blood cell count) before ASCT have been associated with higher RR [52]. Importantly, data from our transplantation center show that MRD detection after 1 course of consolidation chemotherapy was an independent prognostic factor for 3-year OS (83.1% versus 19.0%; $P = .006$) and DFS (73.9% versus 14.2%; $P = .049$) in patients with AML who underwent ASCT in CR1 [18].

Yoon et al [21] monitored *AML1/ETO* and *CBFB/MYH11* through a more sensitive molecular method based on qPCR and found a higher 3-year RR in patients expressing higher levels of pre-ASCT MRD markers. Similarly, Qin et al [41] reported that a *CBFB/MYH11* level of >.2% after 2 courses of consolidation was an independent prognostic factor for poor OS, DFS, and cumulative incidence of relapse in autografted patients. High expression of Wilms' tumor gene 1 (*WT1*) in leukapheresis of peripheral blood autografts pre-ASCT has been associated with a high risk of relapse (cutoff value for *WT1*: 80 copies/10^4 ABL; 87% versus 30%; $P = .0001$) [53], consistent with the results published by Yoon et al [21]. In addition, Mule et al [54] reported that individualized MRD parameters, combined with *WT1* and other non-leukemia-specific genes, such as *PRAME* and *MSLN*, can predict prognosis after ASCT in patients with AML with high sensitivity. They monitored MRD in peripheral blood autografts pre-ASCT in a subset of patients with AML and found that *WT1* alone had limited predictive value for the RR, whereas multiparameter MRD [considering inv(16), t(8;21), *NPM1* mutation, *WT1*, *PRAME*, and *MSLN*] was more sensitive for predicting leukemia recurrence, showing 52% sensitivity and 83% specificity for predicting early relapse in

patients with AML who underwent ASCT. Moreover, among 21 patients with specific leukemic-related mutation at diagnosis, no patients with negative MRD relapsed within 1 year after ASCT, whereas 83% of patients with MRD positivity relapsed. Therefore, multiparameter MRD may be reliable for predicting clinical outcomes, and the expression levels of *WT1, PRAME*, and *MSLN* in autografts could be used to predict early relapse after ASCT in patients with AML.

With advancements in cytogenetics, molecular genetics, and immunology, major breakthroughs in the field of MRD have been made. In addition, with the application of more sensitive methods, such as qPCR, MFC, and next-generation sequencing, MRD is becoming more important for evaluating the curative effects of therapy and selecting treatment plans [55]. Overall, the data support ASCT as a promising approach that can yield impressive survival outcomes in patients with negative MRD pre-ASCT.

Conditioning Regimens

BuCy is a standard conditioning regimen for ASCT in patients with AML. Researchers have recently attempted to replace Cy with drugs showing stronger antileukemia effects and lower extrahematologic toxicity to yield novel conditioning regimens, including BuMel. BuMel was first applied as a conditioning regimen in 129 adult patients with AML in CR1 [28]. In these patients, the 8-year projected OS and DFS were 62% and 56%, respectively; the main extrahematologic toxicity was mucositis, without significant impairment of hepatic, renal, or pulmonary function; and NRM was only 4.65% [28]. These results are consistent with findings reported by Neglar et al [22], who retrospectively compared the clinical outcomes of ASCT following different conditioning regimens based on Bu, including Bu (12.8 mg/kg) with Cy (120 mg/kg), Bu with Mel (140 mg/m^2), Bu with etoposide, and Bu with idarubicin (IDA). In multivariate analysis, BuMel was associated with the superior OS. Gorin et al [23] reported that in patients with AML who underwent ASCT in CR1, those conditioned with BuMel showed better RR, LFS, and OS than those who received BuCy, and NRM was similar in the 2 groups. In a subsequent study, Gorin et al [27] reported an interaction between BuMel conditioning regimens and high-risk AML. In a larger patient population with primary AML autografted in CR1, patients with high-risk AML were found to benefit most from ASCT with a BuMel conditioning regimen, yielding lower 5-year RR and better LFS and OS. Although the authors also demonstrated these benefits of BuMel in multivariate analyses, BuMel treatment was not an independent prognostic factor for patients in the good- and intermediate-risk groups [27]. Data from Japan also indicated that a BuCy ± etoposide or BuMel regimen was associated with superior antileukemic effects (in terms of LFS, OS, and NRM) compared with other Bu-based regimens and TBI-based myeloablative regimens in children with AML who underwent ASCT [56].

IDA+Bu (I-Bu) may be a feasible conditioning regimen for patients with AML who receive ASCT. Hong et al [57] retrospectively analyzed the outcomes of 32 patients with AML who underwent ASCT in CR1 with an I-Bu conditioning regimen (IDA 20 mg/m^2/day × 3, Bu 3.2 mg/m^2/day × 4 i.v. or 4.0 mg/m^2/day × 4 orally). Of these 32 patients, 31 achieved hematopoietic reconstruction, and at a median follow-up of 30 months, 24 were still alive and 20 continued in CR; the 2-year RR was 40%, and the median DFS and OS had not been reached. Ferrara et al [44] reported impressive survival outcomes in 99 patients with AML who underwent ASCT after I-Bu, with a median OS and DFS of 34 and 22 months, respectively, for all patients.

Overall, these results demonstrate that Bu-based conditioning regimens, particularly BuMel, are associated with superior antileukemia effects compared with other Bu-based and TBI-based regimens, and that clinical outcomes of ASCT with an I-Bu regimen are favorable in patients with AML. Further studies, including randomized trials in large populations, are needed to determine the optimal conditioning regimen.

CD34$^+$ Cell Count and Other Factors Influencing Hematologic Recovery

Peripheral blood stem cell transplantation (PBSCT) is associated with more rapid hematologic recovery, shorter hospitalization, and similar OS and DFS compared with bone marrow stem cell transplantation [9,28,58,59]. Although some data have indicated that PBSCT is associated with higher RR [60], numerous studies have demonstrated that high RR is correlated with high CD34$^+$ cell count, regardless of the stem cell source. The number of infused CD34$^+$ cells can also affect clinical outcomes [61]. Several studies have shown no significant differences in OS, LFS, and RR in patients who undergo ASCT with peripheral blood or bone marrow as the stem cell source [2,23,26]. Low CD34$^+$ cell counts ($<2.0 \times 10^6$/kg) are not conducive to engraftment [62], and higher CD34$^+$ cell counts ($>7.16 \times 10^6$/kg) are related to higher RR [63], which may be caused by remnants of leukemia in the autograft. Therefore, the number of infused CD34$^+$ cells is a key factor affecting hematopoietic reconstitution and outcomes after ASCT. In a phase II prospective study in patients with AML in CR1, autografted patients who received $>7.1 \times 10^6$/kg CD34$^+$ cells showed poor OS [64]. In a separate study, higher yields of CD34$^+$ cells ($\geq 7 \times 10^6$/kg) were associated with an inferior prognosis owing to a significantly higher RR [65]. Grubovic et al [66] demonstrated that neutrophil engraftment is correlated with the number of transplanted CD34$^+$ cells and mononuclear cells, but not with platelet engraftment. Therefore, clinical outcomes after ASCT in patients with AML are significantly affected by CD34$^+$ cell counts.

CONCLUSION

Our review indicates that, based on the reported data, for patients with favorable- and intermediate-risk AML in CR1 and patients with APL in CR2, ASCT is feasible when an MSD is not available. Advanced age is not an absolute contraindication. MRD status pre-ASCT is a main factor to consider when determining whether a patient is eligible for ASCT and can effectively predict clinical outcomes after ASCT. Although the best conditioning regimen has not yet been determined, BuMel has been shown to have significant antileukemia effects and low toxicity in autografted patients, even those with high-risk AML. With the improvement of survival outcomes in patients with AML following ASCT, the recommendation for ASCT should be revisited. Recurrence of leukemia is the first and foremost concern when considering ASCT; therefore, researchers are currently exploring approaches to reduce the risk of leukemia recurrence after ASCT. Prospective trials evaluating different conditioning regimens and outcomes in patients with varying molecular cytogenetics are urgently needed. In addition, further studies are needed to evaluate the impact of molecular-targeted therapeutic drugs, such as midostaurin, enasidenib, and venetoclax, on ASCT [67–70].

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REFERENCES

1. Bertoli S, Tavitian S, Huynh A, et al. Improved outcome for AML patients over the years 2000-2014. *Blood Cancer J*. 2017;7:635.
2. Saraceni F, Bruno B, Lemoli RM, et al. Autologous stem cell transplantation is still a valid option in good- and intermediate-risk AML: a GITMO survey on 809 patients autografted in first complete remission. *Bone Marrow Transplant*. 2017;52:163–166.
3. Gorin NC, Labopin M, Pabst T, et al. Unrelated matched versus autologous transplantation in adult patients with good and intermediate risk acute myelogenous leukemia in first molecular remission. *Am J Hematol*. 2017;92:1318–1323.
4. Simancikova I, Bojtarova E, Hrubisko M, et al. Autologous hematopoietic stem cell transplantation for acute myeloid leukemia—single- center experience. *Neoplasma*. 2017;64:738–744.
5. Cornelissen JJ, Versluis J, Passweg JR, et al. Comparative therapeutic value of post-remission approaches in patients with acute myeloid leukemia aged 40-60 years. *Leukemia*. 2015;29:1041–1050.
6. Vellenga E, van Putten W, Ossenkoppele GJ, et al. Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. *Blood*. 2011;118:6037–6042.
7. Heini AD, Berger MD, Seipel K, et al. Consolidation with autologous stem cell transplantation in first remission is safe and effective in AML patients above 65 years. *Leuk Res*. 2017;53:28–34.
8. Burnett AK, Goldstone AH, Stevens RM, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. *Lancet*. 1998;351:700–708.
9. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med*. 1995;332:217–223.
10. Schlenk RF, Taskesen E, van Norden Y, et al. The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant CEBPA. *Blood*. 2013;122:1576–1582.
11. Limvorapitak W, Barnett MJ, Hogge DE, et al. Outcomes of intermediate risk karyotype acute myeloid leukemia in first remission undergoing autologous stem cell transplantation compared with allogeneic stem cell transplantation and chemotherapy consolidation: a retrospective, propensity-score adjusted analysis. *Clin Lymphoma Myeloma Leuk*. 2018;18: e481–e491.
12. Mizutani M, Hara M, Fujita H, et al. Comparable outcomes between autologous and allogeneic transplant for adult acute myeloid leukemia in first CR. *Bone Marrow Transplant*. 2016;51:645–653.
13. Keating A, DaSilva G, Pérez WS, et al. Autologous blood cell transplantation versus HLA-identical sibling transplantation for acute myeloid leukemia in first complete remission: a registry study from the Center for International Blood and Marrow Transplantation Research. *Haematologica*. 2013;98:185–192.
14. Saraceni F, Labopin M, Gorin NC, et al. Matched and mismatched unrelated donor compared to autologous stem cell transplantation for acute myeloid leukemia in first complete remission: a retrospective, propensity score-weighted analysis from the ALWP of the EBMT. *J Hematol Oncol*. 2016;9:79.
15. Gorin NC, Labopin M, Piemontese S, et al. T-cell-replete haploidentical transplantation versus autologous stem cell transplantation in adult acute leukemia: a matched pair analysis. *Haematologica*. 2015;100:558–564.
16. Chen J, Yang L, Fan Y, et al. Comparison of autologous stem cell transplantation versus haploidentical donor stem cell transplantation for favorable- and intermediate-risk acute myeloid leukemia patients in first complete remission. *Biol Blood Marrow Transplant*. 2018;24:779–788.
17. Chevallier P, Labopin M, Socie G, et al. Comparison of umbilical cord blood allogeneic stem cell transplantation vs. auto-SCT for adult acute myeloid leukemia patients in second complete remission at transplant: a retrospective study on behalf of the SFGM-TC. *Eur J Haematol*. 2015;94:449–455.
18. Yao J, Zhang G, Liang C, et al. Combination of cytogenetic classification and MRD status correlates with outcome of autologous versus allogeneic stem cell transplantation in adults with primary acute myeloid leukemia in first remission. *Leuk Res*. 2017;55:97–104.
19. Yoon JH, Kim HJ, Park SS, et al. Long-term clinical outcomes of hematopoietic cell transplantation for intermediate-to-poor-risk acute myeloid leukemia during first remission according to available donor types. *Oncotarget*. 2017;8:41590–41604.
20. Mizutani M, Takami A, Hara M, et al. Comparison of autologous and unrelated transplants for cytogenetically normal acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2017;23:1447–1454.
21. Yoon JH, Kim HJ, Park SS, et al. Clinical outcome of autologous hematopoietic cell transplantation in adult patients with acute myeloid leukemia: who may benefit from autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2017;23:588–597.
22. Nagler A, Labopin M, Gorin NC, et al. Intravenous busulfan for autologous stem cell transplantation in adult patients with acute myeloid leukemia: a survey of 952 patients on behalf of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2014;99:1380–1386.
23. Gorin NC, Labopin M, Czerw T, et al. Autologous stem cell transplantation for adult acute myelocytic leukemia in first remission—Better outcomes after busulfan and melphalan compared with busulfan and cyclophosphamide: a retrospective study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Cancer*. 2017;123:824–831.
24. Eom KS, Kim HJ, Cho BS, et al. Equivalent outcome of autologous stem cell transplantation and reduced-intensity conditioning stem cell transplantation in acute myeloid leukemia patients with t(8;21). *Acta Haematol*. 2015;133:266–276.
25. Gorin NC, Labopin M, Meloni G, et al. Impact of FLT3 ITD/NPM1 mutation status in adult patients with acute myelocytic leukemia autografted in first remission. *Haematologica*. 2013;98:e12–e14.
26. Helbig G, Kocleęga A, Woźniczka K, Kopera M, Kyrcz-Krzemień S. Long-term outcome of autologous hematopoietic stem cell transplantation (AHSCT) for acute myeloid leukemia (AML): a single-center retrospective analysis. *Pathol Oncol Res*. 2018;24:469–475.
27. Gorin NC, Labopin M, Blaise D, et al. Optimizing the pretransplant regimen for autologous stem cell transplantation in acute myelogenous leukemia: better outcomes with busulfan and melphalan compared with busulfan and cyclophosphamide in high-risk patients autografted in first complete remission: a study from the Acute Leukemia Working Party of the EBMT. *Am J Hematol*. 2018;93:859–866.
28. Lemoli RM, D'Addio A, Marotta G, et al. BU/melphalan and auto-SCT in AML patients in first CR: a Gruppo Italiano Trapianto di Midollo Osseo (GITMO) retrospective study. *Bone Marrow Transplant*. 2010;45:640–646.
29. Cioch M, Jawniak D, Wach M, et al. Autologous hematopoietic stem cell transplantation for adults with acute myeloid leukemia. *Transplant Proc*. 2016;48:1814–1817.
30. Mueller BU, Seipel K, Bacher U, Pabst T. Autologous transplantation for older adults with AML. *Cancers (Basel)*. 2018:10:E340.
31. Miyamoto T, Nagafuji K, Fujisaki T, et al. Prospective randomization of post-remission therapy comparing autologous peripheral blood stem cell transplantation versus high-dose cytarabine consolidation for acute myelogenous leukemia in first remission. *Int J Hematol*. 2018;107:468–477.
32. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute myeloid leukemia, version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15:926–957.
33. Yanada M, Tsuzuki M, Fujita H, et al. Phase 2 study of arsenic trioxide followed by autologous hematopoietic cell transplantation for relapsed acute promyelocytic leukemia. *Blood*. 2013;121:3095–3102.
34. Yanada M, Yano S, Kanamori H, et al. Autologous hematopoietic cell transplantation for acute promyelocytic leukemia in second complete remission: outcomes before and after the introduction of arsenic trioxide. *Leuk Lymphoma*. 2017;58:1061–1067.
35. Lengfelder E, Lo-Coco F, Ades L, et al. Arsenic trioxide-based therapy of relapsed acute promyelocytic leukemia: registry results from the European LeukemiaNet. *Leukemia*. 2015;29:1084–1091.
36. Ganzel C, Mathews V, Alimoghaddam K, et al. Autologous transplant remains the preferred therapy for relapsed APL in CR2. *Bone Marrow Transplant*. 2016;51:1180–1183.
37. Thirugnanam R, George B, Chendamarai E, et al. Comparison of clinical outcomes of patients with relapsed acute promyelocytic leukemia induced with arsenic trioxide and consolidated with either an autologous stem cell transplant or an arsenic trioxide-based regimen. *Biol Blood Marrow Transplant*. 2009;15:1479–1484.
38. Holter Chakrabarty JL, Rubinger M, Le-Rademacher J, et al. Autologous is superior to allogeneic hematopoietic cell transplantation for acute promyelocytic leukemia in second complete remission. *Biol Blood Marrow Transplant*. 2014;20:1021–1025.
39. de Botton S, Fawaz A, Chevret S, et al. Autologous and allogeneic stem-cell transplantation as salvage treatment of acute promyelocytic leukemia initially treated with all-trans-retinoic acid: a retrospective analysis of the European acute promyelocytic leukemia group. *J Clin Oncol*. 2005;23: 120–126.
40. Gorin NC, Labopin M, Frassoni F, et al. Identical outcome after autologous or allogeneic genoidentical hematopoietic stem-cell transplantation in first remission of acute myelocytic leukemia carrying inversion 16 or

t(8;21): a retrospective study from the European Cooperative Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2008;26:3183–3188.
41. Qin YZ, Xu LP, Chen H, et al. Allogeneic stem cell transplant may improve the outcome of adult patients with inv(16) acute myeloid leukemia in first complete remission with poor molecular responses to chemotherapy. *Leuk Lymphoma*. 2015;56:3116–3123.
42. Kuwatsuka Y, Miyamura K, Suzuki R, et al. Hematopoietic stem cell transplantation for core binding factor acute myeloid leukemia: t(8;21) and inv (16) represent different clinical outcomes. *Blood*. 2009;113:2096–2103.
43. Appelbaum FR, Kopecky KJ, Tallman MS, et al. The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. *Br J Haematol*. 2006;135:165–173.
44. Ferrara F, Izzo T, Criscuolo C, et al. Favorable outcome in patients with acute myelogenous leukemia with the nucleophosmin gene mutation autografted after conditioning with high-dose continuous infusion of idarubicin and busulfan. *Biol Blood Marrow Transplant*. 2010;16:1018–1024.
45. Ma Y, Wu Y, Shen Z, Zhang X, Zeng D, Kong P. Is allogeneic transplantation really the best treatment for FLT3/ITD-positive acute myeloid leukemia? A systematic review. *Clin Transplant*. 2015;29:149–160.
46. Bornhäuser M, Illmer T, Schaich M, et al. Improved outcome after stem-cell transplantation in FLT3/ITD-positive AML. *Blood*. 2007;109:2264–2265. author reply 2265.
47. Palmieri S, Ferrara F, Leoni F, et al. Myeloablative chemotherapy followed by autologous stem cell infusion may overcome the adverse prognostic impact of FLT3 (foetal liver tyrosine kinase 3) mutations in patients with acute myeloid leukaemia and normal karyotype. *Hematol Oncol*. 2007;25:1–5.
48. Guièze R, Cornillet-Lefebvre P, Lioure B, et al. Role of autologous hematopoietic stem cell transplantation according to the NPM1/FLT3-ITD molecular status for cytogenetically normal AML patients: a GOELAMS study. *Am J Hematol*. 2012;87:1052–1056.
49. Majhail NS, Bajorunaite R, Lazarus HM, et al. High probability of long-term survival in 2-year survivors of autologous hematopoietic cell transplantation for AML in first or second CR. *Bone Marrow Transplant*. 2011;46:385–392.
50. Mollee P, Gupta V, Song K, et al. Long-term outcome after intensive therapy with etoposide, melphalan, total body irradiation and autotransplant for acute myeloid leukemia. *Bone Marrow Transplant*. 2004;33:1201–1208.
51. Maurillo L, Buccisano F, Del Principe MI, et al. Toward optimization of postremission therapy for residual disease-positive patients with acute myeloid leukemia. *J Clin Oncol*. 2008;26:4944–4951.
52. Terwijn M, van Putten WL, Kelder A, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. *J Clin Oncol*. 2013;31:3889–3897.
53. Messina C, Candoni A, Carrabba MG, et al. Wilms' tumor gene 1 transcript levels in leukapheresis of peripheral blood hematopoietic cells predict relapse risk in patients autografted for acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2014;20:1586–1591.
54. Mulé MP, Mannis GN, Wood BL, et al. Multigene measurable residual disease assessment improves acute myeloid leukemia relapse risk stratification in autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:1974–1982.
55. Buckley SA, Appelbaum FR, Walter RB. Prognostic and therapeutic implications of minimal residual disease at the time of transplantation in acute leukemia. *Bone Marrow Transplant*. 2013;48:630–641.
56. Sakaguchi H, Muramatsu H, Hasegawa D, et al. Comparison of conditioning regimens for autologous stem cell transplantation in children with acute myeloid leukemia: a nationwide retrospective study in Japan. *Pediatr Blood Cancer*. 2019;66:e27459.
57. Hong M, Miao R, Zhang R, et al. High-dose idarubicin plus busulfan as conditioning regimen to autologous stem cell transplantation: promising post-remission therapy for acute myeloid leukemia in first complete remission. *Med Oncol*. 2014;31:980.
58. Reiffers J, Labopin M, Sanz M, et al. Autologous blood cell vs marrow transplantation for acute myeloid leukemia in complete remission: an EBMT retrospective analysis. *Bone Marrow Transplant*. 2000;25:1115–1119.
59. Isidori A, Bonifazi F, Visani G, Gherlinzoni F, Baccarani M, Lemoli RM. Autologous stem cell transplantation for acute myeloid leukemia patients in first complete remission: a 10-year follow-up study of 118 patients. *Haematologica*. 2005;90:139–141.
60. Gorin NC, Labopin M, Blaise D, et al. Higher incidence of relapse with peripheral blood rather than marrow as a source of stem cells in adults with acute myelocytic leukemia autografted during the first remission. *J Clin Oncol*. 2009;27:3987–3993.
61. Hengeveld M, Suciu S, Chelgoum Y, et al. High numbers of mobilized $CD34^+$ cells collected in AML in first remission are associated with high relapse risk irrespective of treatment with autologous peripheral blood SCT or autologous BMT. *Bone Marrow Transplant*. 2015;50:341–347.
62. Villalón L, Odriozola J, Laraña JG, et al. Autologous peripheral blood progenitor cell transplantation with $<2 \times 10(6)$ CD34(+)/kg: an analysis of variables concerning mobilisation and engraftment. *Hematol J*. 2000;1:374–381.
63. Gorin NC, Labopin M, Reiffers J, et al. Higher incidence of relapse in patients with acute myelocytic leukemia infused with higher doses of $CD34^+$ cells from leukapheresis products autografted during the first remission. *Blood*. 2010;116:3157–3162.
64. Capelli D, Chiarucci M, Poloni A, et al. Mobilization-driven postconsolidation therapy in elderly patients with acute myeloid leukemia: feasibility and efficacy of autologous stem cell transplantation versus low-dose gemtuzumab ozogamicin. *Biol Blood Marrow Transplant*. 2014;20:1399–1406.
65. Keating S, Suciu S, de Witte T, et al. The stem cell mobilizing capacity of patients with acute myeloid leukemia in complete remission correlates with relapse risk: results of the EORTC-GIMEMA AML-10 trial. *Leukemia*. 2003;17:60–67.
66. Grubovic RM, Georgievski B, Cevreska L, Genadieva-Stavric S, Grubovic MR. Analysis of factors that influence hematopoietic recovery in autologous transplanted patients with hematopoietic stem cells from peripheral blood. *Open Access Maced J Med Sci*. 2017;5:324–331.
67. Lynn RC, Poussin M, Kalota A, et al. Targeting of folate receptor ß on acute myeloid leukemia blasts with chimeric antigen receptor-expressing T cells. *Blood*. 2015;125:3466–3476.
68. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354–365.
69. Lichtenegger FS, Krupka C, Köhnke T, Subklewe M. Immunotherapy for acute myeloid leukemia. *Semin Hematol*. 2015;52:207–214.
70. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. *Br J Haematol*. 2016;175:496–504.