Review Article

Is There Still a Role for Stem Cell Transplantation in Multiple Myeloma?

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High-dose chemotherapy and autologous stem cell transplantation (ASCT) are a standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (MM). The introduction of novel agents, which range from immunomodulatory drugs and proteasome inhibitors to monoclonal antibodies and have now been integrated into both induction and salvage regimens, has dramatically revolutionized the treatment landscape of MM and challenged the role of high-dose chemotherapy and ASCT in treating MM. These advances have led to a number of provocative questions. First, what is the current role of stem cell transplantation (SCT) in comparison with standard-dose therapy incorporating novel agents? Second, should ASCT be performed upfront ("early") or later ("delayed") in the course of the disease? Third, should single or double ASCT be performed? Fourth, is allogeneic SCT still an option for patients with MM? This article provides an overview of available data and evidence-based responses regarding the role of SCT in MM. ***Cancer* 2019;0:1-10**. © *2019 American Cancer Society.*

KEYWORDS: allogeneic, autologous, multiple myeloma, novel agents, transplant.

INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy and the most common indication for autologous stem cell transplantation (ASCT) in the United States.[1,2]

The natural history of MM was first changed by the introduction of high-dose chemotherapy and ASCT,[3,4] and it was then further improved by the use of novel agents such as the immunomodulatory drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide, the proteasome inhibitors (PIs) bortezomib, carfilzomib, and ixazomib, and, most recently, the monoclonal antibodies elotuzumab and daratumumab.[5,6] These therapeutic innovations have led to a significant survival improvement, with the median overall survival (OS) of patients with MM now ranging from 6 to 10 years and depending on the age of the patients at diagnosis.[2,7]

Because of the wide availability of new targeted therapies for the treatment of MM, the role of stem cell transplantation (SCT) has been questioned in recent years, with several trials addressing the role and timing of transplantation.

In this article, we provide an overview of the available literature on the use of SCT for treating patients with MM.

SCT FOR PATIENTS WITH NEWLY DIAGNOSED MYELOMA

ASCT Eligibility

High-dose melphalan followed by autologous stem cell rescue is currently a worldwide standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM).[8,9] In Europe, chronological age has been used to define ASCT eligibility, particularly in clinical trials, with 65 years as a cutoff for defining ASCT-eligible and -ineligible patients. However, a recent analysis of both the European Blood and Marrow Transplantation (EBMT) and Center for International Blood and Marrow Research registries clearly showed a constant increase, from 1991-1995 to 2010, in the use of ASCT in older patients (older than 65 years).[10,11]

The feasibility of high-dose melphalan and ASCT in older patients has been evaluated in several studies.[12-14] In a prospective study enrolling patients older than 65 years, ASCT, conditioned with melphalan at 100 mg/m^2, was demonstrated to be feasible and effective (5-year OS, 63%), especially among patients aged 66 to 70 years, whose treatment-related mortality (TRM) was lower than that of patients older than 70 years (5% vs 19%).[15] In the DSSM II trial, in which patients underwent tandem ASCT conditioned with melphalan at 140 mg/m^2, no difference in terms of TRM (1%) was reported between patients aged 60 to 65 years and those older than 65 years.[16] In another prospective trial

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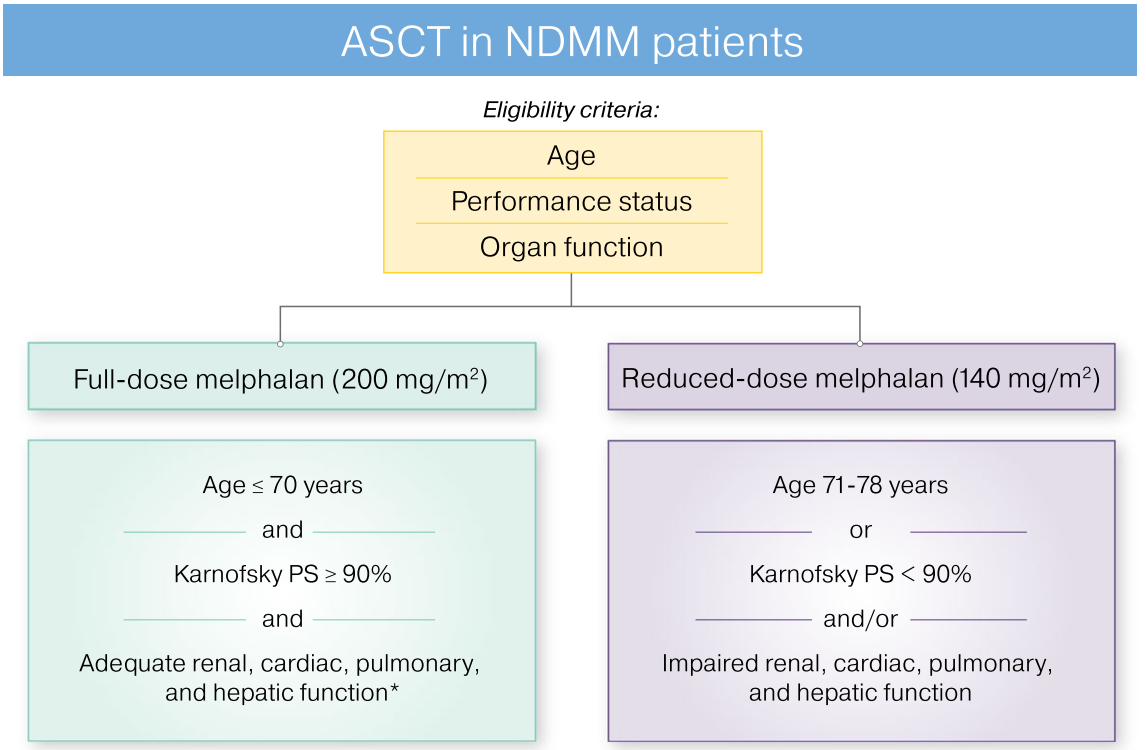

Figure 1. ASCT in patients with NDMM. *Glomerular filtration rate >60 mL/min (renal function); left ventricular ejection fraction >40% (cardiac function); diffusion capacity of carbon monoxide/forced expiratory volume in 1 second >40% to 80% (pulmonary function); and bilirubin level <1.5 × ULN and aspartate aminotransferase/alanine aminotransferase level <2.5 × ULN (hepatic function). ASCT indicates autologous stem cell transplantation; NDMM, newly diagnosed multiple myeloma; PS, performance status; ULN, upper limit of normal.

comparing melphalan at 140 mg/m^2 with melphalan at 200 mg/m^2 in patients older than 65 years, the TRM rate at day +100 from transplantation was 0% in both arms, and this confirmed the feasibility of delivering high-dose melphalan to older patients.[17]

Many studies have confirmed that chronological age is not itself a limitation for ASCT. Instead, organ function and comorbidities as well as the performance status should be taken into consideration to define ASCT eligibility,[18] and currently in the United States, ASCT is considered and may be appraised for patients up to the age of 80 years (Fig. 1).

ASCT Versus Non–Transplant-Based Strategies

The first 2 large trials to compare high-dose chemotherapy and ASCT with standard-dose chemotherapy were conducted by the Intergroup Francophone du Myèlome (IFM) and the Medical Research Council (Table 1).[3,4] In both trials, high-dose chemotherapy and ASCT significantly prolonged progression-free survival (PFS) and OS in comparison with standard-dose chemotherapy without transplantation. It should be noted that, at the time, limited salvage options were available for these patients, and this accounted for the early improvement in OS in both trials.

Several trials were conducted thereafter to support the benefit of high-dose chemotherapy and ASCT in comparison with standard-dose chemotherapy, although only 1 trial was able to detect a significant OS advantage among patients undergoing ASCT.[23-27] However, all the studies comparing ASCT with standard-dose chemotherapy that were published before 2010 did not include novel agents as part of the initial treatment of patients with NDMM. With the incorporation of IMiDs and PIs in the upfront treatment of patients with MM, the need for ASCT as part of the first-line treatment has, therefore, been challenged.

To date, 4 phase 3 trials have compared high-dose chemotherapy and ASCT with novel agent–based regimens without ASCT. The first study, published by Palumbo et al[19] (RV-MM-209), enrolled 402 patients with NDMM who, after a lenalidomide and

TABLE 1. Phase 3 Studies Comparing ASCT and Nontransplant Approaches Based on Novel Agents

Source	Study Design	Response	PFS, Median	OS, Median
Palumbo 2014[19]	MPR × 6 cycles vs high-dose melphalan + ASCT (×2)	—	43 vs 22 mo $P < .001$	4 y: 82% vs 65% $P = .02$
Gay 2015[20]	CRD × 6 cycles vs high-dose melphalan + ASCT (×2)	—	43 vs 29 mo $P < .001$	4 y: 86% vs 73% $P = .004$
Cavo 2016[21]	VMP × 4 cycles vs high-dose melphalan + ASCT (×1 vs ×2)	≥VGPR: 86% vs 74% $P < .001$	3 y: 66% vs 58% $P = .037$	—
Attal 2017[22]	RVD × 5 cycles vs high-dose melphalan + ASCT (×1) + RVD × 2 cycles	CR: 59% vs 48% $P < .001$	50 vs 36 mo $P < .001$	4 y: 81% vs 82% P = NS

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; CRD, cyclophosphamide, lenalidomide, and dexamethasone; MPR, melphalan, prednisone, and lenalidomide; NS, not significant; OS, overall survival; PFS, progression-free survival; RVD, lenalidomide, bortezomib, and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone.

dexamethasone (Rd) induction, were randomized to either 2 courses of high-dose melphalan (200 mg/m^2) followed by ASCT or 6 cycles of melphalan, prednisone, and lenalidomide (MPR). Patients in the ASCT arm had significantly longer PFS (median, 43 vs 22 months; $P < .001$) and a higher 4-year OS rate (82% vs 65%; $P = .02$). Similar results were presented by Gay et al[20] in the EMN-441 phase 3 trial, in which 389 patients with NDMM, treated with Rd induction, were randomized to undergo either tandem ASCT or 6 cycles of cyclophosphamide, lenalidomide, and dexamethasone (CRD). Again, patients in the ASCT group displayed a prolonged median PFS (43 vs 29 months; $P < .001$) and a higher 4-year OS rate (86% vs 73%; $P = .004$) in comparison with patients in the no-ASCT arm. In a pooled analysis of the 2 trials, the advantage of ASCT versus a lenalidomide-based approach without ASCT in terms of 5-year PFS (55% vs 45%; $P = .01$), progression-free survival 2 (PFS2; 71% vs 62%; $P = .02$), and OS (87% vs 71%; $P = .03$) was confirmed also in patients with a complete response (CR).[28]

The addition of bortezomib to Rd (lenalidomide, bortezomib, and dexamethasone [RVD]) significantly improved the median PFS (43 vs 30 months; $P = .002$) and OS (75 vs 64 months; $P = .025$) in comparison with Rd alone. Therefore, RVD has become a standard of care for patients with NDMM.[29]

A formal comparison of ASCT and RVD was performed in the IFM 2009 trial. Seven hundred patients, after 3 RVD induction cycles, were randomized to 1 course of high-dose melphalan (200 mg/m^2) and ASCT followed by 2 further RVD cycles or 5 RVD cycles without ASCT, and all patients received lenalidomide maintenance. A higher rate of CR (59% vs 48%; $P = .03$) and minimal residual disease negativity (79% vs 65%; $P < .001$) among patients in the ASCT arm was observed, and this translated into a 35% reduction in the risk of progression or death (median PFS, 50 vs 36 months; hazard ratio, 0.65; $P < .001$) in favor of transplant patients in comparison with those who received RVD only. No difference in terms of OS was noted at 4 years; however, a longer follow-up might be needed to highlight an OS difference between the 2 arms, especially in light of the wealth of salvage treatment options that may cloud the OS benefit.[22] Moreover, in all trials, PFS has been improved with early ASCT, and this suggests an improved depth of response and better disease control for most patients.

In the European EMN02/HO95 trial, which compared 1 or 2 courses of melphalan at 200 mg/m^2 and ASCT with bortezomib, melphalan, and prednisone (VMP) consolidation after a bortezomib-based induction, patients randomized to the ASCT group displayed a higher rate of at least a very good partial response (VGPR; 86% vs 74%; $P < .001$) and a higher 3-year PFS rate (66% vs 58%; $P = .037$) in comparison with patients in the VMP arm.[21]

All the trials comparing ASCT with novel agent–based treatments without transplantation for patients with NDMM that have been conducted so far continue to favor ASCT over a nontransplant approach in terms of high-quality responses and PFS, with 2 trials also reporting a significant OS advantage for patients undergoing ASCT. For these reasons, ASCT still remains the standard of care for transplant-eligible patients with newly diagnosed myeloma.

Early ASCT Versus Delayed ASCT

Before the introduction of novel agents, the role of early ASCT in comparison with delayed ASCT was addressed in 3 trials. In the study published by Fermand et al,[24] a trend toward better PFS ($P = .07$) and a longer interval without treatment, symptoms, and treatment-related toxicities was observed for early ASCT over delayed ASCT,

TABLE 2. Select Studies Comparing Single and Double ASCT

Source	Study Design	PFS, Median	OS, Median
Attal 2003[34]	Mel at 140 mg/m^2 + TBI at 8 Gy + ASCT vs Mel at 140 mg/m^2 + ASCT1 → Mel at 140 mg/m^2 + TBI at 8 Gy + ASCT2	25 vs 36 mo *P* = .03	48 vs 58 mo *P* = .1
Fermand 2003[35]	Mel at 140 mg/m^2 + ASCT vs Mel at 140 mg/m^2 + ASCT1 → Mel at 140 mg/m^2 + VP16 + TBI at 12 Gy + ASCT2	31 vs 33 mo —	—
Cavo 2007[36]	Mel at 200 mg/m^2 + ASCT vs Mel at 200 mg/m^2 ASCT1 → Mel at 140 mg/m^2 + Bu at 1 mg/kg + ASCT2	25 vs 35 mo *P* = .01	65 vs 71 mo *P* = .9
Mai 2016[37]	Mel at 200 mg/m^2 + ASCT × 1 vs Mel at 200 mg/m^2 + ASCT × 2	25 vs 29 mo *P* = NS	75 vs 79 mo *P* = NS
Cavo 2016[38]	Mel at 200 mg/m^2 + ASCT × 1 vs Mel at 200 mg/m^2 + ASCT1 × 2	45 mo vs NR 3 y: 60% vs 73% *P* = .03	—
Stadtmauer 2016[39]	Mel at 200 mg/m^2 + ASCT1 → lenalidomide maintenance vs Mel at 200 mg/m^2 + ASCT × 2 → lenalidomide maintenance	38 mo: 57% vs 52% *P* = NS	38 mo: 82% vs 83% *P* = NS

Abbreviations: ASCT, autologous stem cell transplantation; ASCT1, first autologous stem cell transplantation; ASCT2, second autologous stem cell transplantation; Bu, busulphan; Mel, melphalan; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; VP16, etoposide.

but there was no OS advantage. A North American cooperative study comparing high-dose therapy and ASCT with standard-dose therapy offered delayed ASCT to patients in the standard-dose arm; approximately 50% of these patients with follow-up underwent ASCT at relapse. At 7 years, the OS was equal for the patients in the 2 arms (38% vs 39%).[26] From the randomized CIAM study, which was specifically designed to compare early and delayed ASCT, a preliminary analysis, reported in abstract form, showed no OS difference between the 2 arms.[30]

Two retrospective analyses compared early ASCT (within 12 months of the diagnosis) and delayed ASCT (beyond 12 months). Kumar et al[31] analyzed 290 patients treated with an IMiD-based induction who subsequently underwent ASCT. They showed similar median times to progression (TTPs) from ASCT (20 vs 16 months; *P* = not significant) as well as no difference in terms of 4-year OS (73% in both groups) with early and delayed ASCT. However, the reasons for delayed ASCT are not clear, and a higher percentage of patients in the delayed ASCT group had deeper responses to induction therapy. Furthermore, this analysis may have limited value because of the short TTP in both arms. Similar results were reported by Dunavin et al[32] in an analysis of 167 patients undergoing early or delayed ASCT; despite a trend toward a longer median TTP in the early ASCT group (28 vs 23 months; *P* = .055), no differences in terms of OS were noted between the 2 groups at 3 (90% vs 82%) and 5 years (63% vs 63%). Again, the median TTP was shorter than those seen in trials with modern maintenance approaches.

These trials showed the feasibility of delayed ASCT; however, because of the lack of randomization and the absence of stratification for baseline characteristics, it is not clear which subgroup of patients can actually benefit the most from delayed ASCT.

In a pooled analysis of the RV-MM-209 and EMN-441 studies, only 53% of the patients who did not undergo ASCT as part of their first-line treatment were able to undergo ASCT at relapse. Patients who underwent ASCT upfront not only had longer PFS but also benefited from longer 4-year PFS2 (71% vs 54%; $P < .001$) and OS (84% vs 70%; $P < .001$) in comparison with those who underwent delayed ASCT.[33] It must be noted that the patients in the nontransplant arm were treated with a suboptimal induction and consolidation (Rd-MPR/CRD) approach in comparison with current 3-drug regimens including a PI and an IMiD.

Nonetheless, this pooled analysis shows that a fraction of patients who do not undergo ASCT upfront may not be able to undergo it at relapse. A possible explanation for this phenomenon is related to the aging of patients, the deterioration of their performance status and comorbid conditions, and the type of relapse. However, in the more recent IFM 2009 trial, a higher proportion of patients (79%) who did not undergo ASCT upfront were instead able to undergo salvage autologous stem cell transplantation (sASCT), and this probably is reflected in the lack of OS observed between the 2 arms. Longer follow-up is needed to evaluate the impact of delayed ASCT on PFS2 and OS.[22]

Single ASCT Versus Tandem ASCT

The role of tandem ASCT as an upfront treatment in patients with NDMM and its superiority over single ASCT have been investigated with conflicting results, and this still remains a matter of discussion (Table 2).

The first evidence of the superiority of tandem ASCT over single ASCT came from the IFM study

published in 2003, which demonstrated longer median event-free survival (36 vs 25 months; $P = .03$) and OS (58 vs 48 months; $P = .01$) in patients undergoing tandem ASCT. In a subgroup analysis, the authors reported that the patients who benefited the most from tandem ASCT were those who failed to achieve a VGPR after the first ASCT, which may be expected because the induction therapy did not include novel agents.[34]

In the Italian trial published by Cavo et al,[36] patients undergoing tandem ASCT had a higher rate of CR (47% vs 33%) and significantly prolonged median event-free survival (35 vs 23 months; $P = .001$) but similar OS (median, 71 vs 65 months; $P = .9$) in comparison with patients who underwent single ASCT. Similarly, in a randomized study by Fermand et al[35] conducted in patients with NDMM, double ASCT has yet to show an OS advantage over single ASCT. Sonneveld et al[40] compared a nonmyeloblative approach (2 cycles of melphalan at 70 mg/m^2) with the same regimen followed by ASCT in a phase 3 study; despite a higher CR rate (32% vs 13%; $P < .001$) and prolonged median PFS (27 vs 24 months; $P = .006$), no difference in OS (50 vs 55 months) was observed between the 2 arms.

More recently, in a pooled analysis of 4 European trials, the median PFS was longer (50 vs 38 months; $P < .001$) and the 5-year OS rate was higher (75% vs 63%; $P = .002$) in patients receiving a second transplant in comparison with patients for whom a single ASCT was planned.[41]

Similar results have been reported in a preliminary analysis of the European EMN02/HO95 trial, in which patients who underwent tandem ASCT had a significantly higher 3-year PFS rate (74% vs 62%; $P = .005$) in comparison with those who underwent single ASCT.[38]

To address the role of consolidation therapy after a first ASCT, the phase 3 STAMINA trial randomized patients with NDMM who previously underwent a first ASCT to either a second ASCT or RVD consolidation followed by lenalidomide maintenance.[39] At 38 months, the investigators found no differences in terms of PFS (57% vs 57%) or OS (86% vs 82%) between the 2 groups.

If we take into consideration the conflicting results published so far, a second ASCT appears to be a feasible and reasonable option, especially for patients with high-risk MM and those who fail to achieve at least a VGPR after the first transplant. Ongoing and future randomized trials should ultimately define the role of tandem ASCT in the general population.

Early Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation (allo-SCT) is regarded as a potentially curative approach for MM because of the graft-versus-myeloma effect mediated by the donor immune system.[42] However, despite its biological rationale, the role of allo-SCT in the treatment of MM is limited.

Two meta-analyses including studies that compared allo-SCT with ASCT as the initial treatment for NDMM failed to demonstrate the superiority, in terms of PFS and OS, of allo-SCT over ASCT; this was despite higher rates of CR among patients in the allo-SCT group, who also experienced higher TRM than the ASCT group, and early and late relapses continue to be a major cause of treatment failure.[43,44]

To combine a highly effective cytoreductive procedure yet take advantage of the graft-versus-myeloma effect, a tandem ASCT/mini-allo-SCT approach, using a reduced-intensity conditioning (RIC) regimen, was designed, and it was compared with the standard tandem ASCT approach for the initial treatment of patients with myeloma (Table 3).

In 2 trials only, both of which were not randomized and were designed before the novel agent era, patients who underwent tandem ASCT/allo-SCT had a clear PFS and OS advantage in comparison with patients undergoing tandem ASCT. These results were not confirmed by other studies, in which neither PFS nor OS was prolonged with ASCT/allo-SCT in comparison with tandem ASCT.[45-52] Notably, the majority of those trials did not incorporate the use of novel agents into the induction and consolidation/maintenance phase.

To date, allo-SCT is not routinely recommended as part of the initial treatment of patients with NDMM because of the increased toxicity and the lack of a clear benefit for most patients. However, for young, selected, and motivated patients with high-risk MM, allogeneic transplantation may be considered, preferentially in the context of a clinical trial.[8,9]

SALVAGE SCT FOR PATIENTS WITH RELAPSED AND/OR REFRACTORY MYELOMA

sASCT

Several retrospective studies have evaluated the role of sASCT in the relapse setting, and they have demonstrated that ASCT for a second or even third time is a feasible and effective treatment option among patients who have previously undergone ASCT.[53-55]

TABLE 3. Select Studies Comparing Tandem ASCT and Autologous/Allogeneic Reduced-Intensity Conditioning Stem Cell Transplantation in Patients With NDMM

Source	Population	Conditioning Regimens		Follow-Up, Median, mo	PFS, Median	OS, Median	TRM
		ASCT	Allo-SCT				
Garban 2006[45] Moreau 2008[46]	Patients with NDMM with del13 and B2M >3 mg/dL	Mel200, Mel220	Bu and Flu	56	22 vs 19 mo $P = .58$	48 vs 34 mo $P = .07$	NA vs 11%
Bjorkstrand 2011[47] Gahrton 2013[48]	Patients with NDMM	Mel200	Flu and TBI at 200 CGy	86	8 y: 12% vs 22% $P = .027$	8 y: 39% vs 49% $P = .03$	3 y: 3% vs 13%
Bruno 2007[49] Giaccone 2011[50]	Patients with NDMM	Mel200	TBI at 200 cGy	96	35 vs 29 mo $P = .02$	80 vs 54 mo $P = .01$	2% vs 10%
Rosinol 2008[51]	Patients with NDMM not in nCR/CR after 1st ASCT	Mel200 or CVB	Flu and Mel	62	31 mo vs NR $P = .08$	58 mo vs NR $P = .9$	5% vs 16%
Krishnan 2011[52]	Patients with NDMM after prior ASCT	Mel200	TBI at 200 cGy	40	3 y: 46% vs 43% $P = .7$	3 y: 80% vs 71% $P = .2$	NA

Abbreviations: allo-SCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B2M, β_2-microglobulin; Bu, busulphan; CR, complete response; CVB, cyclophosphamide, etoposide, and carmustine; del13, deletion 13q; Flu, fludarabine; Mel200, melphalan at 200 mg/m^2; Mel220, melphalan at 220 mg/m^2; NA, not available; nCR, nearly complete response; NDMM, newly diagnosed multiple myeloma; NR, not reported; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; TRM, treatment-related mortality.

A retrospective analysis of the EBMT registry showed that sASCT was safe (1-year nonrelapse mortality [NRM], 2%) and effective (3-year OS, 46%). This study also demonstrated that patients with a long relapse-free interval from their previous ASCT (>36 months) had longer PFS ($P = .045$) and OS ($P = .019$) in comparison with patients with a shorter relapse-free interval (<36 months).[56]

Similar results were confirmed in a retrospective analysis by Lemieux et al,[57] in which 93% of the patients achieved at least an objective response after sASCT, with 46% of them reaching a VGPR. No treatment-related deaths were observed, and the median PFS after sASCT was 18 months. Again, the duration of response from previous ASCT (>24 months) was associated with longer PFS and OS.

In a matched-pair analysis comparing sASCT with conventional chemotherapy in patients previously treated with ASCT, sASCT significantly extended the median OS (56 vs 25 months; $P = .04$) in comparison with conventional chemotherapy.[58]

The only prospective evaluation of sASCT has been conducted in the context of the Myeloma X trial; at relapse, after a bortezomib-based re-induction, patients were randomized to sASCT or cyclophosphamide. sASCT significantly extended median PFS (19 vs 11 months; $P < .001$), but not OS (65 vs 56 months; $P = .19$), in comparison with cyclophosphamide. However, the use of salvage cyclophosphamide alone is not considered a standard treatment approach because of the wide availability of novel agents at relapse.[59]

A retrospective analysis showed that a sASCT was safe (TRM, 6%) and effective (CR rate, 44%; median PFS, 14 months) even in patients who received maintenance therapy after upfront ASCT.[60]

These studies have demonstrated that sASCT is a safe and effective treatment option for patients with relapsed and refractory MM. Both the American and European guidelines regard sASCT as a feasible treatment option for relapsed patients with previous adequate stem cell collection.[8,9,61]

However, because of the growing number of effective antimyeloma drugs, it is important to carefully select those patients who might benefit the most from sASCT (eg, prolonged remission from first ASCT and adequate performance status).

Salvage Allo-SCT

Data on allo-SCT in the relapse setting are scarce and are mainly provided by retrospective analyses and single-center institutions. A European analysis of the EBMT registry on the use of allo-SCT among patients with MM showed a steady increase in the use of allo-SCT, particularly later in the course of the disease, with a parallel increase in the use of RIC over myeloablative conditioning. Among 3405 patients with MM undergoing allo-SCT after ASCT, the 5-year PFS and OS rates were 15% and 32%, respectively, whereas the NRM rate was 29%; this confirmed high toxicity and relapse rates with limited benefit.[62]

In a retrospective study including 169 patients with MM who had relapsed after their first ASCT, 68 patients who had an available donor and underwent RIC allo-SCT were compared with 94 patients without a donor.[63] At 2 years, PFS was prolonged in the donor group (42%) in comparison with the no-donor group (18%; $P < .001$) but at a the cost of a significantly higher incidence of

NRM (22% vs 1%; $P < .001$). This was likely reflected in the lack of an OS difference between the 2 groups (54% vs 53%; $P = .33$).

Freytes et al[64] evaluated 289 patients undergoing either ASCT for a second time or allo-SCT after their first ASCT. At 1 year, NRM was significantly higher in the allo-SCT group than the second ASCT group (13% vs 2%; $P < .001$), whereas the 3-year PFS (6% vs 12%) and OS rates (20% vs 46%) were higher among patients undergoing ASCT for a second time.

Kroger et al[65] showed allo-SCT to be effective as a salvage treatment for patients relapsing after ASCT, with an overall response rate at day +100 after transplantation of 95%, which included 46% of the patients achieving a CR. Notably, NRM was significantly lower in patients with human leukocyte antigen–matched SCT in comparison with patients with mismatched SCT (10% vs 53%; $P = 0.001$). At 5 years, the PFS rate was 20%, although 41% of the matched patients with a CR were alive and free from progression. This study demonstrates that a careful selection of patients and donors can optimize the efficacy and safety of allo-SCT, yet it does not make a sufficiently convincing case for allo-SCT in the salvage setting.

To date, there is no clear advantage for salvage allo-SCT over ASCT, particularly when we consider the constantly improving treatment armamentarium and the availability of targeted drugs and immunological approaches for treating MM. Thus, the role of allo-SCT at relapse remains limited to clinical trials.

SCT FOR PATIENTS WITH HIGH-RISK MM

MM is characterized by a variety of recurrent cytogenetic and molecular abnormalities. Of them, t(4;14), t(14;16), t(14;20), del17p, -gain of 1q and 1p deletion have been associated with a poor prognosis.[66]

In a pooled analysis of 4 European phase 3 trials, high-risk patients, defined as those harboring either t(4;14) or del17p or failing to achieve a CR after the induction phase, greatly benefited from tandem ASCT in comparison with patients who underwent a single ASCT in terms of both PFS (median, 42 vs 21 months; hazard ratio, 0.41; $P = .006$) and 5-year OS (70% vs 17%; hazard ratio, 0.22; $P < .001$).[41]

More recently, a subset analysis of patients with high-risk MM treated in the context of the EMN02/HO95 trial showed a positive impact on PFS of double ASCT versus single ASCT (hazard ratio, 5.7; $P = .024$). This, however, is in contrast with the STAMINA trial, which demonstrated no benefit from tandem ASCT, even among high-risk patients. A possible explanation for this discrepancy lies in the different induction regimens of the 2 studies: bortezomib, cyclophosphamide, and dexamethasone in the EMN02/HO95 study and RVD (predominantly) in the STAMINA trial. The different induction therapy may at least partially account for the PFS benefit seen in the European trial in favor of tandem ASCT. At present, the benefit of tandem ASCT for high-risk patients remains unclear, particularly if RVD induction is used.

To evaluate the role of allo-SCT in patients with high-risk fluorescence in situ hybridization, Roos-Weil et al[67] conducted a retrospective analysis of 143 patients with MM who underwent allo-SCT either as part of the initial strategy or as salvage treatment, and they compared their outcomes with those of standard-risk patients. The authors found no difference in the 3-year PFS rate (30% vs 17%; $P = .9$), relapse rate (53% vs 75%; $P = .9$), or OS rate (45% vs 39%; $P = .8$) between patients with high- and standard-risk fluorescence in situ hybridization. TRM was 25% at 2 years, and 47% and 43% of the patients developed any-grade acute and chronic graft-versus-host disease, respectively. Interestingly, the occurrence of chronic graft-versus-host disease was associated with prolonged PFS. In the study conducted by the IFM and including high-risk patients, no PFS/OS benefit was observed in patients undergoing tandem ASCT or ASCT/allo-SCT.[46]

Kroger et al[65] retrospectively analyzed the outcomes of 73 patients with high-risk myeloma treated with either tandem ASCT or tandem ASCT/allo-SCT; although no significant differences were noted in terms of the molecular remission rate (50% vs 40%) or 5-year PFS (24% vs 30%; $P = .7$) between the 2 groups, patients in the tandem ASCT/allo-SCT group had significantly higher 1-year NRM (23% vs 2%) than those in the tandem ASCT group.

On the basis of these data, the International Myeloma Working Group recommended the consideration of tandem ASCT for NDMM with high-risk cytogenetic features.[66] Allo-SCT, though not routinely recommended, may be considered for young patients with high-risk MM in the context of a clinical trial.

In conclusion, even in the era of novel agents, ASCT remains a standard of care for transplant-eligible patients with NDMM. ASCT improves the depth and quality of responses and prolongs survival in comparison with standard-dose therapy; it is, therefore, an essential component of a complex treatment strategy that integrates the use of novel agents in induction and consolidation/maintenance with high-dose chemotherapy and ASCT. Taking

into consideration the efficacy and safety of ASCT, as well as data from randomized studies showing that a significant proportion of patients might not undergo ASCT at relapse, we recommend performing ASCT as part of the initial treatment because the disease is never as sensitive as it is at the time of presentation. However, a plan for delayed ASCT at first relapse, with early stem cell harvesting, for young patients without high-risk myeloma may be considered on the basis of a patient's preferences. The limited benefit of tandem ASCT over single ASCT remains unclear. The most robust data suggest that high-risk patients and patients with a suboptimal response after the first ASCT might benefit from a second transplant, although they are most likely to get a greater benefit from newer consolidation and maintenance approaches.[68] At relapse, sASCT represents an effective treatment option; however, given the wide availability of new drugs, physicians should consider the type and duration of response obtained after prior ASCT to select those patients who will benefit the most from sASCT. Currently, there are no data to support the use of upfront allo-SCT. At relapse, allo-SCT may be considered as a treatment option for high-risk, young, and motivated patients in the context of a clinical trial. However, newer immune-, antibody-, and cellular-based approaches will likely be used early in the course of the disease to eradicate clones of resistant disease.

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