The Evolving Role of Transplantation in Multiple Myeloma: the Need for a Heterogeneous Approach to a Heterogeneous Disease

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Abstract: Autologous stem cell transplant (ASCT) is an established frontline standard of care for the younger, fitter patients with newly diagnosed multiple myeloma (NDMM) who are eligible for the procedure, and has contributed to improved overall survival. In the current era of novel therapies, the treatment landscape and prognosis have changed. The outstanding efficacy seen with regimens based on novel agents has led to a questioning of the frontline treatment paradigm with respect to ASCT. A key current question is whether to use transplant early or to collect stem cells early but save ASCT for salvage therapy. In this review, we evaluate the clinical data for each approach as well as the arguments in favor of early or delayed ASCT. We also consider the clinical/clonal heterogeneity of myeloma and review the evidence regarding which patient subgroups may benefit most from each approach. We summarize current treatment guidelines for transplant-eligible patients with NDMM and review the evolving role of minimal residual disease evaluation and its potential effect on the debate over early vs delayed ASCT. We conclude that frontline ASCT remains a standard of care for a substantial proportion of patients; however, delayed/salvage ASCT is increasingly being used in the context of highly active frontline regimens based on novel agents and the ongoing personalization of myeloma treatment.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, with an estimated 30,770 new cases and 12,770 deaths in 2018 in the United States,[1] and 38,928 new cases and 24,287 deaths in 2012 in Europe.[2] The median age of patients at diagnosis is 69 to 72 years,[3,4] and it is estimated that approximately two-thirds of patients are older than 65 years.[5] Thus, MM is predominantly

a disease of the elderly, and age and patient frailty are important factors when frontline therapy is considered.

High-dose melphalan supported by autologous stem cell transplant (ASCT) has been an established standard of care in the frontline setting for eligible patients for more than 20 years.[6-8] Transplant-eligible patients are typically those up to 65 to 70 years of age who are free of comorbidities that might contraindicate the procedure.[4] The introduction and widespread adoption of ASCT have contributed to the improved overall survival (OS) seen during the past 2 decades in younger, fitter patients with MM.[9-13] However, the improvements in OS that have occurred during the past 2 decades have also been associated with the introduction of multiple novel agents,[9-11,14] including proteasome inhibitors,[15] immunomodulatory drugs,[16] a histone deacetylase inhibitor,[17] and, most recently, monoclonal antibodies.[18,19] Thus, in the current era of novel therapies, the treatment landscape and prognosis have changed, with the median OS improving to 7 to 10 years and multiple treatment options becoming available to patients across all age groups.[8,14,20,21] Moreover, the importance of optimal induction and the use of continuous therapy are now well established, and a role for maintenance therapy, either with or without ASCT, is emerging.[8,22]

With these developments and with the outstanding efficacy of combination regimens based on novel agents seen in patients with newly diagnosed MM (NDMM),[23-25] clinicians are questioning whether the introduction of novel agents is changing the frontline treatment paradigm with respect to ASCT.[21,26-30] Rather than regarding ASCT as the default standard of care for eligible patients, the treatment algorithm in some cases may be evolving to reflect that used for other hematologic malignancies, such as Hodgkin lymphoma, in which frontline chemotherapy results in prolonged disease control (and potential cure) and ASCT is reserved as salvage therapy for those in whom frontline treatment fails.[31] In this review, we evaluate the evidence in favor of early ASCT as part of frontline therapy and the evidence in favor of delayed ASCT as a component of salvage treatment, within the context of current and anticipated future treatment options. We also consider the heterogeneous nature of MM and the various treatment approaches potentially required in different patient subgroups. Further, we review emerging data on the prognostic importance of minimal residual disease (MRD) status and consider how this may affect ASCT treatment decisions, and we look ahead at the future utility of ASCT in MM.

The Case for Frontline ASCT

Summary of Clinical Data

ASCT was established as the standard of care for eligible patients with NDMM by 7 randomized clinical trials (RCTs) conducted in the 1990s and early 2000s,[32-38] which clearly demonstrated the benefit of ASCT vs conventional chemotherapy in this setting. In 5 of the 7 studies,[32,33,36-38] a superior complete response (CR) rate translated into a significant benefit in terms of progression-free survival (PFS). However, the benefit in terms of OS was less clear. The superiority of ASCT was significant in only 3 of the 7 studies,[32,35,38] probably owing to the availability of active salvage treatment options—including salvage ASCT—in the control arms. This issue was specifically addressed by Fermand and colleagues, who conducted an RCT to assess the optimal timing of ASCT, comparing early vs late transplant.[37] The frontline use of ASCT vs conventional chemotherapy resulted in a significant event-free survival (EFS) benefit (median EFS, 39 vs 13 months), but OS was similar in the patients receiving ASCT up front and those who received it at relapse (median OS, 64.6 vs 64.0 months). A subsequent meta-analysis incorporating 9 RCTs of ASCT vs conventional chemotherapy confirmed these findings; the risk for progression was reduced by 25% with ASCT (hazard ratio [HR], 0.75), whereas the risk for death was reduced by only 8% (HR, 0.92).[39] However, all the RCTs in this analysis were conducted in the era before novel agents and before the use of consolidation and maintenance strategies. It has to be considered that before the advent of novel therapies, effective salvage options after initial treatment failure were both fewer and less effective than those now available, implying that this change in the treatment landscape may be of particular importance going forward.[28]

Since the introduction of novel agents, the benefit of ASCT-based vs non–ASCT-based approaches in NDMM has been demonstrated in a number of RCTs (Table 1), thus reinforcing the case for the continued use of ASCT as a component of standard-of-care therapy in eligible patients. The incorporation of novel agents into MM therapy has resulted in improved induction regimens through the integration of proteasome inhibitor–based and immunomodulatory drug–based therapy, as well as the successful development of combination therapies for induction, consolidation, and maintenance.[28] For example, in a phase 3 study by the Italian GIMEMA group (Gruppo Italiano Malattie Ematologiche dell'Adulto), patients received lenalidomide (Revlimid, Celgene)/dexamethasone (Rd) for 4 cycles and were then randomly assigned to undergo ASCT with melphalan conditioning at 200 mg/m^2 or to receive conventional-dose melphalan in combination with prednisone and lenalidomide (MPR) as consolidation; patients were then re-randomized to lenalidomide maintenance or placebo.[40] Both PFS and OS from first randomization were significantly prolonged in the ASCT arm, and patients who underwent ASCT and

Table 1. Studies and Analyses of ASCT-Based vs Non–ASCT-Based Frontline Treatment Approaches for Multiple Myeloma, and of Early vs Late (Salvage) Use of ASCT, in the Era of Novel Agents

Study	Induction	Consolidation	N	Maintenance	ORR	CR	PFS	OS
ASCT-based vs non–ASCT-based frontline treatment								
GIMEMA RV-MM-209[40]	Rd × 4 cycles	MEL200 vs MPR	141 vs 132	R or placebo	NR	NR	43.0 vs 22.4 mo; HR, 0.44	81.6% vs 65.3% at 4 y
GIMEMA RV-MM-EMN-441[41]	Rd × 4 cycles	MEL200 vs RCd	127 vs 129	RP or R	NR	NR	43.3 vs 28.6 mo; HR, 0.40	86% vs 73% at 4 y
Pooled analysis of above 2 studies[42]	Rd × 4 cycles	MEL200 vs MPR/RCd	268 vs 261	RP/R/placebo	NR	NR	PFS1: 42 vs 24 mo; HR, 0.53 PFS2: 71% vs 54% at 4 y; HR, 0.53	84% vs 70% at 4 y; HR, 0.51
IFM/DFCI 2009[7]	RVd × 3 cycles	MEL200 + RVd × 2 cycles vs RVd × 5 cycles	350 vs 350	R for 1 y	99% vs 98%	59% vs 48%	50 vs 36 mo; HR, 0.65	81% vs 82% at 4 y
EMN02/HO95[46]	VCd × 3 or 4 cycles	MEL200 vs VMP × 4 cycles	695 vs 497	RVd vs no consolidation, then R	≥VGPR: 84% vs 75%	NR	64% vs 57% at 3 y; HR, 0.76	No difference evident (85% at 3 y, both arms); data not yet mature
ECOG-ACRIN E4A03[74]	RD/Rd × 4 cycles	Early ASCT vs continued Rd	90 vs 341	None	NR	NR	NR	80% vs 57% at 5 y; HR, 0.55
Early vs late/salvage use of ASCT								
Dunavin et al[51]	Novel agent–based	Early (within 12 mo) vs late MEL200	102 vs 65	None	99% vs 97%	50% vs 28%	28 vs 18 mo; 32% vs 28% at 3 y	NR vs 75 mo; 90% vs 82% at 3 y
Kumar et al[58]	Thalidomide/lenalidomide-based	Early (within 12 mo) vs late MEL200	173 vs 112	NR	92% vs 87% post-ASCT	35% vs 37% post-ASCT	25.4 vs 26.0 mo (TTP)	73% at 4 y in both groups

ACRIN, American College of Radiology Imaging Network; ASCT, autologous stem cell transplant; CR, complete response; DFCI, Dana-Farber Cancer Institute; ECOG, Eastern Cooperative Oncology Group; EMN, European Myeloma Network; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; HR, hazard ratio; IFM, Intergroupe Francophone du Myélome; MEL200, melphalan at 200 mg/m^2 conditioning plus ASCT; mo, months; MPR, melphalan, prednisone, lenalidomide; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, lenalidomide; RCd, lenalidomide, cyclophosphamide, dexamethasone; Rd/RD, lenalidomide plus (low-dose/high-dose) dexamethasone; RP, lenalidomide/prednisone; RVd, lenalidomide, bortezomib, dexamethasone; TTP, time to progression; VCd, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; y, years.

then received lenalidomide maintenance had the longest PFS and OS from diagnosis. Similar findings were seen in a separate phase 3 Italian study of ASCT vs lenalidomide plus cyclophosphamide and dexamethasone (RCd),[41] as well as in a subsequent pooled analysis of these 2 studies (Table 1).[42]

However, the GIMEMA study did not incorporate a proteasome inhibitor in either regimen. Combinations of proteasome inhibitors with immunomodulatory drugs and dexamethasone are some of the most active combination regimens investigated in MM to date, with substantial efficacy seen in the ASCT,[43] non-ASCT,[24] and relapsed[44,45] settings. Additionally, proteasome inhibitors have demonstrated specific synergy with alkylating

agents. Therefore, 2 phase 3 studies have been conducted in transplant-eligible patients with NDMM in which these regimens were used to determine whether ASCT retains its beneficial effect on long-term outcomes (Table 1). In the French portion of the IFM/DFCI (Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute) 2009 phase 3 study (Autologous Transplantation for Multiple Myeloma in the Era of New Drugs),[7] 700 patients with NDMM received 3 cycles of Rd plus bortezomib (Velcade, Millennium/Takeda Oncology; RVd) followed either by ASCT with melphalan 200 mg/m^2 conditioning and 2 further cycles of RVd or by 5 further cycles of RVd. A significantly higher CR rate and significantly longer PFS were demonstrated in the ASCT arm, but OS rates at 4 years were similar in the 2 arms.[7] Also in the French portion of the study, all patients received lenalidomide maintenance for 1 year. In contrast, in the US portion of the study lenalidomide is being continued until disease progression; the results of the US portion of the study are yet to be reported. Meanwhile, preliminary findings have been reported from the EMN02/HO95 study (Study to Compare VMP With HDM Followed by VRD Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma), in which 1192 patients received 3 or 4 cycles of bortezomib, cyclophosphamide, and dexamethasone (VCd) as induction followed either by ASCT with melphalan conditioning at 200 mg/m^2 or by 4 cycles of bortezomib, melphalan, and prednisone (VMP).[46] As in the IFM/DFCI study, a higher rate of deep responses and a higher PFS rate at 3 years were reported. No difference in OS rates has been seen to date, although the data are not yet mature. A second randomization to consolidation therapy vs no consolidation was performed after intensification therapy, to be followed by lenalidomide maintenance until progression or toxicity, in both arms. Double randomization may be a limitation of this study, as the trial may be relatively underpowered in terms of its ability to identify subsets of patients who may or may not benefit from early vs delayed ASCT.

Thus, the available data on ASCT vs non-ASCT approaches in patients with NDMM indicate a consistent PFS benefit from using frontline ASCT and, in some instances, an OS benefit with this approach. In other studies, a lack of OS benefit may be explained by the influence of subsequent therapy (or lack of available options), or potentially by data immaturity. However, beyond these clinical data, other arguments can be made regarding the benefits of frontline ASCT.

Potential Benefits of Frontline ASCT

An ASCT-based approach in eligible patients appears to be an option for potential long-term disease control in a fraction of patients, whereas similar data have not yet been reported for a non–ASCT-based approach. Therefore, there is an argument for employing frontline ASCT to enable the potential for prolonged disease control. Barlogie and colleagues reported increasing 10-year PFS and CR rates with the Total Therapy program of treatment. These rates reached 33% and 49%, respectively, in the Total Therapy IIIa trial (UARK 2003-33), which incorporated proteasome inhibitor/immunomodulatory drug–based induction and consolidation, tandem ASCT, and maintenance.[47] Increasingly high plateaus of disease control were apparent with the use of this very intensive treatment approach, indicating the potential long-term benefit of employing frontline ASCT in combination with therapies based on novel agents in highly selected patients.

Another benefit of using ASCT in the frontline setting is that it may be most feasible at this stage in a patient's disease course. Following initial therapy, a patient's bone marrow function can also be depleted at the time of relapse, or additional comorbidities may have emerged, thus potentially precluding successful ASCT at salvage. This is suggested by results from a number of frontline studies; for example, in the Italian GIMEMA group study of Rd followed by ASCT or MPR,[40] although it was specified in the protocol that patients who received MPR as frontline treatment should receive salvage ASCT at relapse, only 62.8% actually did so. Similarly, in the separate Italian study of ASCT vs RCd,[41] only 43% of patients in the frontline RCd arm received ASCT at relapse.

An additional argument for using ASCT in the frontline setting is that it has been shown to be a cost-effective approach.[30,48] For example, Pandya and colleagues conducted a retrospective analysis of patients treated at the Mayo Clinic to evaluate the cost-effectiveness of early vs delayed ASCT approaches. They demonstrated lower costs with the early approach ($249,235 vs $262,610; 2012 prices), as well as a greater benefit in terms of quality-adjusted life-years (1.96 vs 1.73). The key variables that influenced the findings included OS with the early ASCT approach and treatment-related mortality.[48] Additionally, Shah and colleagues performed a real-world cost-effectiveness analysis of ASCT vs conventional, nonintensive treatment in patients with NDMM younger than 65 years of age.[49] Driven by the significantly prolonged OS seen in patients who underwent ASCT (median OS, 58 vs 37 months), ASCT was associated with an incremental cost-effectiveness ratio (ICER) of $72,852 per life-year gained, within the willingness-to-pay threshold of $100,000[49]; similar findings have been reported in younger cohorts of patients with NDMM.[50] However, data in this regard from randomized studies are very limited, and results from recent studies are awaited with interest.

A final potential benefit of early ASCT is that it may enable patients to have time off treatment, thanks to the prolonged PFS seen vs conventional therapy.[51] However, this is no longer the case in the era of maintenance therapy or in the context of novel agents, which are generally better tolerated. Nevertheless, ASCT followed by maintenance appears to offer a prolonged period of a potentially less intensive treatment before relapse and salvage therapy compared with no ASCT plus maintenance.[40]

The Case for Delayed ASCT

Summary of Clinical Data

Data from a large number of clinical trials in patients with NDMM support the potential utility of delayed ASCT as salvage therapy at relapse, along with the possibility of very good long-term outcomes with non-ASCT frontline approaches. The feasibility and benefit of ASCT in the relapsed setting were initially demonstrated in several early reports.[52-54] Subsequent studies have also shown that a second ASCT can be used and is active in the relapsed setting following a frontline ASCT,[55-57] thus highlighting that clinicians do not necessarily have to choose between early or later ASCT approaches, but can wait and see. In particular, ASCT at relapse has been reported to result in outcomes similar to those with other potential salvage therapies, and in one analysis, the use of novel agents along with salvage ASCT was associated with improved outcomes vs approaches without novel agents, indicating that these therapies are complementary in the relapsed setting as well as in the frontline setting.[55-57]

These studies do not, however, specifically address the issue of whether ASCT can be "saved" for the relapsed setting and not used as frontline therapy. Similarly, the findings of the studies described in the previous section may demonstrate the benefits of ASCT vs nontransplant approaches as frontline therapy, but they do not evaluate outcomes vs those of patients who subsequently received ASCT as salvage therapy. As noted in the previous section, only the study by Fermand and colleagues addressed outcomes in patients receiving early ASCT vs those in patients receiving conventional frontline therapy followed by ASCT at relapse.[37] The results showed that despite a frontline EFS benefit, OS was similar in the 2 groups of patients, and importantly, this study was conducted before the era of novel agents, which are significantly more active than conventional chemotherapy and generally better tolerated, as previously noted. More recently, a couple of analyses have addressed this issue in the era of novel agents to elucidate the benefit of frontline ASCT vs delayed ASCT (Table 1).

In a retrospective analysis of 167 patients who received induction therapy based on novel agents, the outcomes of the patients who received early ASCT (within 12 months of diagnosis) were compared with those of the patients who received later ASCT. Of the patients who received early ASCT, 73% had received 1 and 27% had received more than 1 prior treatment, and of the patients who received later ASCT, 34% had received 1 and 66% had received more than 1 prior treatment; thus ASCT was not used exclusively as frontline or salvage therapy.[51] The rate of very good partial response or better was higher in the early ASCT group and the median PFS was longer (28 vs 18 months), but the overall differences in PFS and OS between the 2 groups were not significant. A similar analysis in patients who had received specifically thalidomide- or lenalidomide-based induction therapy demonstrated no significant differences between the response rates or outcomes of patients who received early ASCT (within 12 months) and those of patients who received later ASCT.[58]

The lack of OS benefit in these specific studies of early vs later ASCT suggests that deferring ASCT until relapse is a feasible approach for some patients. However, it should be noted that these studies may have involved a selection bias toward later ASCT. That is, only chemosensitive patients who responded well to frontline therapy and then relapsed and who were sufficiently physically fit to undergo ASCT could be included within the later ASCT group. Patients with a poorer prognosis who were not eligible for salvage ASCT and those who died before second-line therapy were excluded, resulting in outcomes for later ASCT that were apparently better than if an "intention-to-treat" approach had been used.

Nevertheless, looking beyond these comparative studies of early vs later ASCT, findings from a number of more current clinical studies of state-of-the-art combinations have shown that the use of frontline treatment approaches based on novel agents may achieve impressive long-term outcomes in transplant-ineligible patients with NDMM or in patients without any immediate plan for ASCT. The depth and duration of responses achieved with triplet combinations made up of immunomodulatory drugs and/or proteasome inhibitors plus glucocorticoids, and the tolerability of these regimens, are now challenging the treatment paradigm consisting of remission induction followed by ASCT in all eligible patients. For example, the phase 3 VISTA trial (Velcade as Initial Standard Therapy in Multiple Myeloma) investigated the VMP triplet as a 12-month frontline treatment regimen in transplant-ineligible patients with NDMM. As well as demonstrating a 30% CR rate, similar to that achieved with transplant-based approaches, the elderly patients in the VMP arm experienced a median time to progression of 2 years,[59] and in a long-term follow-up analysis, the median OS was almost 5 years (56.4

months).[25] Similarly impressive outcomes were reported from the phase 3 FIRST trial (Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide), which investigated the utility of continuous Rd as frontline therapy in transplant-ineligible patients.[23] The median PFS with this approach was longer than 2 years (26.0 months), and the median OS was again almost 5 years (58.9 months).[60] The RVd triplet regimen, which in combination with ASCT demonstrated a PFS benefit vs RVd alone in transplant-eligible patients with NDMM,[7] has also shown substantial activity in the nontransplant setting, including superiority vs Rd.[24] In the SWOG (Southwest Oncology Group) S0777 phase 3 study (Bortezomib With Lenalidomide and Dexamethasone Versus Lenalidomide and Dexamethasone Alone in Patients With Newly Diagnosed Myeloma Without Intent for Immediate Autologous Stem-Cell Transplant), in which a relatively young cohort of non-ASCT patients received 8 cycles of RVd followed by Rd maintenance, the median PFS (43 months) was striking, and the median OS was longer than 6 years (75 months).[24] Similarly, in a small study of patients with NDMM, carfilzomib (Kyprolis, Onyx) plus Rd (KRd) followed by lenalidomide maintenance showed promising frontline activity in a non-ASCT approach; 89% of patients achieved a very good partial response or better, and the overall PFS rate at 18 months was 92%.[61] The results of more recent studies incorporating monoclonal antibodies are especially compelling.

Potential Benefits of Delayed ASCT

As demonstrated by the clinical data previously reviewed, non-ASCT frontline approaches can result in excellent outcomes, suggesting that delaying ASCT is feasible without adversely affecting long-term survival. Data from the IFM 2009 study indicate that this approach may be applicable in a large majority of patients; as of the data cutoff date for the manuscript, 79% of the patients who received second-line therapy had undergone subsequent ASCT.[7] Additionally, a number of other potential benefits accrue from an approach encompassing delayed ASCT. First, patients are spared the acute toxicity and potential treatment-related mortality associated with ASCT. It should be acknowledged, however, that the rate of treatment-related mortality is low, with only 6 treatment-related deaths (1.7%) reported in the ASCT arm of the IFM 2009 trial, although the effect of the nonlethal toxicities inherent to ASCT should not be underestimated.[7] Patients may also avoid the long-term effects of ASCT; these include an increased risk for second primary malignancies arising from lenalidomide maintenance following high-dose melphalan, which has been reported in previous studies, and in particular secondary myelodysplastic syndrome and acute myelogenous leukemia, which appear to be specifically related to melphalan-based therapy.[62] Again, a very low rate of secondary malignancies was reported in the ASCT arm of the IFM 2009 trial, in which lenalidomide maintenance following ASCT was continued for 1 year rather than until disease progression[7]; however, follow-up is currently relatively short to establish long-term toxicity rates.[7,63] Finally, the high costs of ASCT[50] are avoided in patients for whom such consolidation may not be required. Although ASCT has demonstrated its cost-effectiveness associated with OS improvements,[30,48,49] such survival benefits may not be demonstrated in the era of novel agents.[7] Nevertheless, it should be acknowledged that the cost-effectiveness ratios for ASCT and non-ASCT approaches in the novel agent era will also be affected by the high costs of some regimens based on novel agents.[14,64]

The Clinical Heterogeneity of Multiple Myeloma

MM is a highly heterogeneous disease, in which various patient subgroups—defined by a multitude of prognostic factors—have substantially different outcomes.[65-69] Consequently, the debate regarding whether to use early or delayed ASCT should not be considered in the context of the overall patient population, as no single treatment approach is appropriate and optimal in 100% of patients with NDMM.[28,63] Instead, it is important to determine which subgroups will derive the greatest benefit from early or delayed ASCT. The degree of benefit may be driven by a number of different characteristics of the patients, such as fitness/frailty and comorbidities, and by various disease-related factors, in particular the highly complex genetic architecture by which an array of genetic mutations may enhance tumor progression and aggressiveness or result in more indolent disease.[65-68] Different clones with radically different genetics and biological drivers require different treatment approaches to optimize eradication and control. It is also important to consider the clonal evolution of MM during its course and the phenomenon of clonal tiding,[70-72] and how they may affect the choice of early or late ASCT. For example, the use of therapies known to have mutagenic effects may not be optimal in patients with high-risk clones that show greater genomic instability and may thus evolve into more aggressive, treatment-resistant disease. Any antimyeloma therapy will disturb the balance of dominant clones and minor clones in the bone marrow compartment. It will be important for us to improve our understanding of how to exert appropriate selective pressure on the clonal population in individual patients, such as through the early or delayed use of ASCT in the context of different regimens based on novel agents,

to prolong disease control and drive the emergence of an indolent dominant clone.

Previous studies of the utility of early or late ASCT were conducted either before the emergence of our understanding of MM clonal heterogeneity or in the absence of the genetic characterization needed for such subgroup analyses. Nevertheless, limited subgroup analyses from previous studies have provided some indications regarding which patients may derive greater or smaller benefit from an early or delayed ASCT approach. For example, in the GIMEMA RV-MM-209 study (Lenalidomide Melphalan and Prednisone Versus High Dose Melphalan in Newly Diagnosed Multiple Myeloma Patients) of ASCT vs MPR as frontline consolidation after Rd induction, the hazard ratios in favor of ASCT for PFS and OS were 0.30 and 0.49, respectively, in patients with high-risk cytogenetics but 0.49 and 0.70, respectively, in patients with standard-risk cytogenetics. This finding suggests a smaller magnitude of benefit with early ASCT in patients who have standard-risk cytogenetics. Nevertheless, the interaction *P* value was not significant for either PFS or OS.[40] In the retrospective analysis of early vs delayed ASCT by Dunavin and colleagues,[51] a significant PFS benefit was seen with early ASCT in patients who had high-risk cytogenetics (median PFS, 25 vs 11 months; *P*=.049) but not in patients with standard-risk cytogenetics. Similarly, in the GIMEMA RV-MM-EMN-441 study (Cyclophosphamide, Lenalidomide and Dexamethasone Versus Melphalan Followed by Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma Subjects) of frontline ASCT vs RCd consolidation, the magnitude of PFS benefit appeared larger in the patients with high-risk cytogenetics (HR, 3.81) than in those with standard-risk cytogenetics (HR, 2.01), albeit again with a nonsignificant interaction *P* value.[41] By contrast, in the IFM/DFCI 2009 study of RVd plus ASCT vs RVd alone, which incorporated a proteasome inhibitor, the PFS magnitude of benefit appeared less pronounced with ASCT vs RVd in the high-risk cytogenetics subgroup than in patients with standard-risk cytogenetics (*P*=.51 for the interaction). Currently, the International Myeloma Working Group (IMWG) recommends using high-dose therapy plus double ASCT in patients with high-risk cytogenetics, as well as treating them with the combination of a proteasome inhibitor plus lenalidomide or pomalidomide (Pomalyst, Celgene) and dexamethasone,[73] reflecting the activity of the RVd triplet regimen in these patients.

Additionally, in the GIMEMA RV-MM-EMN-441 study, the magnitude of the PFS benefit with ASCT vs RCd appeared greater in patients older than 60 years (HR, 3.92) than in patients 60 years of age or younger (HR, 1.78; interaction *P* value, .04), as well as in patients with International Staging System (ISS) stage I MM (HR, 3.15) than in patients with stage II (HR, 1.97) or stage III (HR, 1.72) MM (interaction *P* value, 0.38).[41] Supporting this finding with respect to patient age, the use of early ASCT vs no early ASCT in the ECOG-ACRIN E4A03 trial (Lenalidomide and Dexamethasone With or Without Thalidomide in Treating Patients With Multiple Myeloma) showed a significant OS benefit in patients 65 years of age or older (HR, 0.42) but not in patients younger than 65 years (HR, 0.79).[74]

These findings provide some insights into the potential for different treatment approaches in the various subgroups of patients with NDMM. However, much more investigation is required before it will be feasible to make clinical recommendations regarding adopting an early vs delayed ASCT approach on the grounds of patient or disease characteristics.

Current Guidelines and Recommendations

Numerous current guidelines and recommendations are available that outline the role and use of ASCT in the settings of frontline treatment and treatment for relapsed MM. Table 2 and the eTable (see hematologyandoncology.net) provide a summary of recommendations from the following organizations: the IMWG alone[75]; the American Society for Blood and Marrow Transplantation (ASBMT), European Society for Blood and Marrow Transplantation (EBMT), and IMWG combined[76]; the ASBMT alone[77]; the National Comprehensive Cancer Network (NCCN)[78]; the European Society for Medical Oncology (ESMO)[4]; and the European Myeloma Network (EMN).[79] A summary of the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) guidelines[80-83] is also included in the eTable. The guidelines predominantly recommend frontline ASCT in eligible patients. A number of the documents, however, acknowledge that many physicians, particularly in the United States, collect stem cells but reserve ASCT for salvage in patients who are doing well with their initial therapy. It is acknowledged in many of the guidelines that the debate regarding the use of early vs late ASCT remains to be resolved in the absence of prospective, comparative studies; however, some recommendations are provided with regard to specific patients in whom a delayed approach may be considered, in accordance with the evidence presented in the previous section of this review.

The Evolving Role of MRD Evaluation

As well as being influenced by patient and disease characteristics, as previously outlined, the discussion regarding early vs late ASCT is beginning to be affected by the evolving role of MRD evaluation in the treat-

Table 2. Key Recommendations for the Use of ASCT in Current Multiple Myeloma Treatment Guidelines (also see eTable)

Guidelines/ Organization	Patient Population	Recommendations as Part of Frontline Therapy	Recommendations as Part of Salvage Therapy
IMWG[75]	All	ASCT is a treatment option that can be performed safely at most specialized transplantation or myeloma centers in selected patients up to the age of 70-75 years who are medically fit. "While final results of [the IFM/DFCI 2009 and EMN02/HO95] studies are awaited, the IMWG recommends that ASCT should be offered at some point in the course of the treatment program for a patient eligible to receive HDT." "[Until] final results… [are] available, ASCT up front should continue to be considered the preferred approach for a patient who is eligible to tolerate HDT."	"Although favorable results with ASCT up front are backed by phase 3 studies, increasing numbers of patients and physicians, particularly in the United States, are currently opting to collect stem cells early and deferring transplantation at the time of relapse." "An alternative choice that can be discussed with the patient, particularly if response to therapy is favorable and he/she is unwilling to proceed to early ASCT, is to continue induction for as long as maximal tumor reduction is achieved and then to maintain response until relapse or progression, at which time salvage ASCT can be performed."
ASBMT[77]	All	"We recommend HDT and ASCT as consolidative therapy for patients with MM (grade A recommendation)." "Based on available prospective data, we continue to recommend early (up-front) ASCT. However, given the recent and rapid changes in induction therapy, it is also reasonable to consider enrollment on a clinical trial that addresses the question of transplantation timing."	"Retrospective studies suggest feasibility of delayed ASCT in the modern era." "We recommend consideration of a first ASCT for patients with refractory disease (grade C)."
NCCN[78]	All	ASCT: "Category 1 evidence supports proceeding straight after induction therapy to HDT and SCT versus saving the SCT for salvage therapy." "Evidence suggests equivalent OS, although PFS can be prolonged by an early transplant."	"Additional ASCT on or off clinical trial is an option depending on the time interval between the preceding SCT and documented progression." "Retrospective studies suggest a 2-3 year minimum length of remission for consideration of a second ASCT for salvage therapy (category 2B)."
EMN[79]	NDMM	"Novel-agent–based induction and up-front ASCT in medically fit patients remains the standard of care."	"In patients who respond well and tolerate induction, initial therapy may be continued after stem cell collection, reserving ASCT for first relapse."

ASBMT, American Society for Blood and Marrow Transplantation; ASCT, autologous stem cell transplant; DFCI, Dana-Farber Cancer Institute; EMN, European Myeloma Network; HDT, high-dose therapy; IFM, Intergroupe Francophone du Myélome; IMWG, International Myeloma Working Group; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; RRMM, relapsed and/or refractory multiple myeloma; SCT, stem cell transplant.

ment of MM. Although currently not widely practiced as standard, the importance of MRD evaluation has been growing over recent years, and the achievement of MRD-negative remission is now regarded as a new goal for MM therapy.[84-87] Numerous studies have demonstrated the prognostic value of MRD status,[84,85,88,89] with MRD negativity strongly associated with prolonged PFS and OS.[90] The increasing sensitivity of MRD evaluation techniques is of importance. For example, one study has demonstrated an OS benefit of approximately 1 year per log reduction in MRD level[91]; thus, the achievement of MRD-negative status by the emerging standard approach of next-generation flow cytometry (sensitivity of $\geq 10^{-5}$) or by next-generation sequencing (sensitivity of 10^{-6}) is of particular prognostic value.[87]

Importantly, clinical data have demonstrated that the long-term remissions and prolonged OS demonstrated among patients achieving MRD-negative status occur

regardless of the treatment modality used to achieve MRD negativity, whether an ASCT[89,91] or non-ASCT approach.[85,92] For example, in the IFM/DFCI 2009 study, although the MRD-negative remission rate was higher in the ASCT arm, PFS and OS were significantly longer in the MRD-negative patients than in the patients who remained MRD-positive, regardless of whether RVd plus ASCT or RVd alone had been the treatment approach.[7] These findings call into question the need for ASCT consolidation in those patients achieving MRD-negative remission in response to highly active frontline therapy based on novel agents.[26,84,86,93] In the absence of data from randomized studies, this question cannot yet be answered; however, designs for such studies have been proposed that use an MRD-driven paradigm for guiding subsequent therapy, including whether to give ASCT consolidation.[84,93] The findings of such studies will be of great value with regard to the debate over early vs delayed ASCT in the context of MRD elimination.

The Future of ASCT in Multiple Myeloma

As increasing numbers of treatment regimens based on novel agents become available, as disease monitoring techniques are becoming increasingly sensitive and more widely used, and as our understanding of MM biology further improves, personalized therapy for patients with NDMM is coming closer. The position of ASCT in the MM treatment algorithm is becoming increasingly complex as it moves away from being a standard-of-care approach in transplant-eligible patients. As acknowledged in the treatment guidelines, a number of physicians are reserving ASCT for salvage in patients who are doing well on their initial therapy, and studies are ongoing or planned to provide clinical data supportive of this approach, particularly in the context of MRD evaluation. Therefore, participation in relevant randomized prospective trials is encouraged as the treatment paradigm continues to evolve and important questions regarding the use of early vs delayed ASCT approaches remain unanswered.[28] A key issue in this context is identifying parameters and/or biomarkers enabling better patient stratification, with the goal of exposing to early ASCT only those who are most likely to benefit from this approach in terms of long-term outcomes. Conversely, ASCT should be reserved for salvage in those who are most likely to derive long-term benefit from continuing frontline therapy based on novel agents, such as patients achieving MRD-negative status. This question will become increasingly complex and relevant in the near future with the emergence and increased use of additional novel targeted therapies for NDMM. These therapies include the monoclonal antibodies daratumumab (Darzalex, Janssen Biotech) and elotuzumab (Empliciti, Bristol-Myers Squibb).[19] Furthermore, in the longer term, novel immunologic approaches, including chimeric antigen receptor (CAR) T-cell therapy, may fundamentally alter the MM treatment algorithm,[94] raising additional questions about the role and timing of ASCT in eligible patients.

In conclusion, frontline ASCT remains a standard of care for a substantial proportion of eligible patients, although the option of delaying ASCT until salvage therapy is required is being increasingly considered in the context of highly active frontline regimens based on novel agents. Ongoing and planned studies will further inform the debate regarding early vs delayed ASCT, with a key aim being to identify the patients most likely to benefit from each approach. Finally, the ongoing evolution of MM management and the emergence of novel treatment options may ultimately obviate the need for frontline ASCT as a standard of care in the context of increasing personalization of treatment.

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Supporting Online Material for "Transplantation in Multiple Myeloma: the Need for a Heterogeneous Approach to a Heterogeneous Disease"

This eTable contains the complete version of Table 2, which appeared in an abbreviated form in the August 2018 issue.

eTable. Recommendations for the Use of ASCT in Current Multiple Myeloma Treatment Guidelines

Guidelines/ Organization	Patient Population	Recommendations as Part of Frontline Therapy	Recommendations as Part of Salvage Therapy
IMWG[75]	All	ASCT is a treatment option that can be performed safely at most specialized transplantation or myeloma centers in selected patients up to the age of 70-75 years who are medically fit. "While final results of [the IFM/DFCI 2009 and EMN02/HO95] studies are awaited, the IMWG recommends that ASCT should be offered at some point in the course of the treatment program for a patient eligible to receive HDT." "[Until] final results… [are] available, ASCT up front should continue to be considered the preferred approach for a patient who is eligible to tolerate HDT."	"Although favorable results with ASCT up front are backed by phase 3 studies, increasing numbers of patients and physicians, particularly in the United States, are currently opting to collect stem cells early and deferring transplantation at the time of relapse." "An alternative choice that can be discussed with the patient, particularly if response to therapy is favorable and he/she is unwilling to proceed to early ASCT, is to continue induction for as long as maximal tumor reduction is achieved and then to maintain response until relapse or progression, at which time salvage ASCT can be performed."
IMWG[73]	High-risk cytogenetics	"HDT plus double ASCT is recommended for patients with high-risk cytogenetics." "Tandem auto-allo-SCT may improve PFS in patients with t(4;14) or del(17p)."	–
ASBMT/EBMT/ IMWG[76]	RRMM	–	"In transplantation-eligible patients relapsing after primary therapy that did NOT include an ASCT, HDT with ASCT as part of salvage therapy should be considered standard." "HDT and ASCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an ASCT with initial remission duration of more than 18 months."
ASBMT[77]	All	"We recommend HDT and ASCT as consolidative therapy for patients with MM (grade A recommendation)." "Based on available prospective data, we continue to recommend early (up-front) ASCT. However, given the recent and rapid changes in induction therapy, it is also reasonable to consider enrollment on a clinical trial that addresses the question of transplantation timing."	"Retrospective studies suggest feasibility of delayed ASCT in the modern era." "We recommend consideration of a first ASCT for patients with refractory disease (grade C)."
NCCN[78]	All	ASCT: "Category 1 evidence supports proceeding straight after induction therapy to HDT and SCT versus saving the SCT for salvage therapy." "Evidence suggests equivalent OS, although PFS can be prolonged by an early transplant."	"Additional ASCT on or off clinical trial is an option depending on the time interval between the preceding SCT and documented progression." "Retrospective studies suggest a 2-3 year minimum length of remission for consideration of a second ASCT for salvage therapy (category 2B)."

(Table continues on following page.)

eTable. ***(Continued)*** Recommendations for the Use of ASCT in Current Multiple Myeloma Treatment Guidelines

Guidelines/ Organization	Patient Population	Recommendations as Part of Frontline Therapy	Recommendations as Part of Salvage Therapy
ESMO[4]	All	"For younger patients (<65 years or fit patients <70 years in good clinical condition), induction followed by HDT with ASCT is the standard treatment [II, B]."	"In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months."
EMN[79]	NDMM	"Novel-agent–based induction and up-front ASCT in medically fit patients remains the standard of care."	"In patients who respond well and tolerate induction, initial therapy may be continued after stem cell collection, reserving ASCT for first relapse."
mSMART/ Rajkumar[80-83]	Standard risk	RVd × 4 cycles, then early ASCT or stem cell cryopreservation and continued RVd × 8-12 cycles or RVd × 4 cycles and Rd to progression.	"Consider salvage ASCT in patients eligible for ASCT who have not had transplant before; consider 2nd ASCT if eligible and >18 mo unmaintained or >36 mo maintained response to 1st ASCT."
	Intermediate/high risk	RVd × 4 cycles, then early ASCT, followed by bortezomib-based or carfilzomib-based maintenance for 2 years.	"Consider salvage ASCT in patients eligible for ASCT who have not had transplant before; consider 2nd ASCT if eligible and >18 mo unmaintained or >36 mo maintained response to 1st ASCT."

ASBMT, American Society for Blood and Marrow Transplantation; ASCT, autologous stem cell transplant; DFCI, Dana-Farber Cancer Institute; EBMT, European Society for Blood and Marrow Transplantation; EMN, European Myeloma Network; ESMO, European Society for Medical Oncology; HDT, high-dose therapy; IFM, Intergroupe Francophone du Myélome; IMWG, International Myeloma Working Group; MM, multiple myeloma; mo, months; mSMART, Mayo Stratification of Myeloma and Risk-Adapted Therapy; NCCN, National Comprehensive Cancer Network; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; RRMM, relapsed and/or refractory multiple myeloma; RVd, lenalidomide, bortezomib, dexamethasone; SCT, stem cell transplant.