The Role of High-Dose Melphalan and Autologous Stem Cell Transplant in the Rapidly Evolving Era of Modern Multiple Myeloma Therapy

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Abstract: The advent of the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide; the proteasome inhibitors bortezomib, carfilzomib, and ixazomib; the histone deacetylase inhibitor panobinostat; and the monoclonal antibodies elotuzumab and daratumumab has led to dramatic improvements in outcomes for patients with multiple myeloma. Along with progress in nontransplant therapy have come questions regarding the continued role of high-dose melphalan (HDM) supported by autologous stem cell transplant (ASCT) in the treatment of multiple myeloma. Emerging evidence from phase 3 studies demonstrates that consolidation therapy with HDM/ASCT further improves depth of response and progression-free survival in the context of modern therapy for multiple myeloma. Moreover, unprecedented survival data from ongoing phase 3 studies of patients treated with modern myeloma therapy followed by HDM/ASCT in first-line or second-line therapy reaffirm single and tandem HDM/ASCT as important standards of care for eligible patients. Herein, we review the evolving role of HDM/ASCT for the treatment of patients with newly diagnosed or relapsed multiple myeloma.

Autologous Stem Cell Transplant: the Standard of Care in Multiple Myeloma

The clinical efficacy of high-dose melphalan (HDM) and the need for such an approach to be supported by autologous hematopoietic stem cell rescue—a combination henceforth referred to as HDM/autologous stem cell transplant (ASCT)—was first noted in the early to mid-1980s.[1-4] Phase 3 studies subsequently emerged that evaluated the efficacy of HDM/ASCT compared with conventional chemotherapy (CCT; Table 1).[5-10] The Intergroupe Français du Myélome (IFM) 90 study randomly assigned patients younger

Table 1. Selected Phase 3 Studies of Conventional Chemotherapy vs High-Dose Melphalan Supported By Autologous Hematopoietic Stem Cell Transplant

Study	CCT Regimen	HDM Induction	HDT	Response Rate		PFS/EFS		OS		Salvage HDM	
				CCT	HDM	CCT	HDM	CCT	HDM	CCT	HDM
Attal,[5] 1996	VMCP alt with BVAP × 18 cycles	VMCP alt with BVAP × 4-6 cycles	Mel 140 mg/m^2 + TBI 8 Gy	CR: 5%, VGPR: 9%	CR: 22%, VGPR: 16%	Median EFS: 18 mo	Median EFS: 27 mo	5-y OS: 12%	5-y OS: 52%	9%	8%
Child,[6] 2003	CVAMP until max response	Induction: CVAMP ≥3 cycles → Mel 200 mg/m^2	Mel 200 mg/m^2 (Mel 140 mg/m^2 + TBI allowed)	CR: 8%	CR: 44%	Median PFS: 19.6 mo	Median PFS: 31.6 mo	Median OS: 42.3 mo	Median OS: 54.1 mo	30%	2%
Barlogie,[7] 2006	VAD × 4 cycles → VBMCP × 1 y	VAD × 4 cycles	Mel 140 mg/m^2 + TBI 12 Gy	CR: 11%	CR: 11%	7-y PFS: 14%	7-y PFS: 17%	7-y OS: 38%	7-y OS: 38%	87 of 157	NR
Bladé,[8,a] 2005	VBMCP/VBAD × 12 cycles	VBMCP/VBAD × 4 cycles	Mel 200 mg/m^2 (Mel 140 mg/m^2 + TBI allowed)	CR: 11%	CR: 30%	Median PFS: 33 mo	Median PFS: 42 mo	Median OS: 66 mo	Median OS: 61 mo	10%	7%
Fermand,[9] 2005	VMCP until stable plateau phase achieved	VAMP × 3-4 cycles	Mel 200 mg/m^2 or Mel 140 mg/m^2 + busulfan 16 mg/kg	CR + MRD 19%	CR + MRD 34%	Median EFS: 19 mo	Median EFS: 25 mo	Median OS: 47.6 mo	Median OS: 47.8 mo	21%	7%

alt, alternating; BVAP, carmustine, vincristine, doxorubicin, prednisone; CCT, conventional chemotherapy; CR, complete response; CVAMP, cyclophosphamide, vincristine, doxorubicin, methylprednisolone; EFS, event-free survival; HDM, high-dose melphalan; Mel, melphalan; MRD, minimal residual disease; mo, month/months; NR, not reported; PFS, progression-free survival; OS, overall survival; TBI, total body irradiation; VAD, vincristine, doxorubicin, dexamethasone; VAMP, vincristine, doxorubicin, methylprednisolone; VBAD, vincristine, carmustine, doxorubicin, dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VGPR, very good partial response; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; y, year/years.

[a] Only patients responding to an initial course of VBMCP/VBAD were evaluated.

than 65 years with Durie-Salmon stage II or III disease to CCT or HDM/ASCT.[5] Seventy-four of 100 patients underwent the planned HDM/ASCT.

Notably, the complete response (CR) was lower for those receiving CCT than those receiving HDM/ASCT (5% vs 22%), as was the very good partial response (VGPR; 9% vs 16%). The median event-free survival (EFS) was 18 months for those assigned to CCT and 27 months for those assigned to HDM/ASCT. The 5-year EFS was 10% with CCT and 28% with HDM/ASCT (P=.03), and 5-year overall survival (OS) was 12% with CCT and 52% with HDM/ASCT (P=.01). For patients aged 60 years or younger, the 5-year OS was lower with CCT than with HDM/ASCT: 18% vs 70% (P=.02). Only 9% of patients in the CCT arm received HDM/ASCT as salvage therapy. The Medical Research Council (MRC) 7 trial randomly assigned 401 patients to CCT or HDM/ASCT.[6] Compared with CCT, HDM/ASCT produced higher CR rates (8% vs 44%; P<.001) and improved median OS (42.3 vs 54.1 months; P=.03) and progression-free survival (PFS, 19.6 months vs 31.6 months; P<.001). Only 15% of patients assigned to CCT received salvage HDM/ASCT. However, other phase 3 studies failed to demonstrate the improvement in OS seen with HDM/ASCT in the IFM and MRC studies, in part owing to differences in study design, choice of CCT, and differences in the rate of salvage SCT for patients assigned to CCT.[7-9] Nonetheless, the majority of these studies confirmed a notable improvement in depth of response and PFS/EFS with HDM/ASCT. Thus, HDM/ASCT became an important standard of care for younger patients with multiple myeloma.

Autologous Stem Cell Transplant in the Era of Novel Agents

The data supporting the use of HDM/ASCT derive from studies enrolling patients between 1990 and 2000, well before regulatory authority approvals of lenalidomide (Revlimid, Celgene), bortezomib (Velcade, Millennium/Takeda Oncology), and, more recently, pomalidomide (Pomalyst, Celgene), carfilzomib (Kyprolis, Onyx), ixazomib (Ninlaro, Millennium/Takeda Oncology), panobinostat (Farydak, Novartis), elotuzumab (Empliciti, Bristol-Myers Squibb), and daratumumab (Darzalex, Janssen). Given the unprecedented efficacy of newer combination treatment strategies, investigators have sought to re-evaluate the value of HDM/ASCT.

Palumbo and colleagues evaluated the efficacy of low-dose melphalan (Evomela, Spectrum), prednisone, and lenalidomide (MPR) consolidation therapy vs HDM/ASCT for newly diagnosed myeloma patients treated with lenalidomide and dexamethasone induction therapy.[11] In a study of 402 patients, 273 were randomly assigned to either tandem ASCT utilizing HDM (200 mg/m^2) or six 28-day cycles of MPR consolidation therapy. Patients underwent a second randomization to lenalidomide maintenance therapy or no maintenance. The median duration of follow-up was 51.2 months. For the 273 patients randomly assigned to MPR or HDM/ASCT, the median PFS was 22.4 and 43.0 months, respectively (hazard ratio [HR], 0.44; *P*<.001), and the 4-year OS was 65.3% and 81.6% (HR, 0.55; *P*=.02). It should be noted that PFS and OS were measured from the date of disclosure of randomization, which occurred after induction therapy and stem cell collection. Among those who went on to receive lenalidomide maintenance therapy, the median PFS from initial enrollment was 34.2 months for those who received MPR vs 54.7 months for those who received HDM/ASCT. Among those who did not go on to receive maintenance therapy, median PFS was 21.8 months for those who received MPR and 37.4 months for those who received HDM/ASCT. The 5-year OS was 70.2% and 78.4% for those receiving MPR and HDM consolidation followed by lenalidomide maintenance therapy, respectively, and 58.7% and 66.6% for those not receiving maintenance therapy (*P* values not provided).

Gay and colleagues conducted a similar study in which patients who had successfully undergone lenalidomide and dexamethasone induction therapy and stem cell collection were randomly assigned to tandem ASCT with HDM (200 mg/m^2) or 6 cycles of cyclophosphamide, lenalidomide, and dexamethasone (CRD).[12] A second randomization occurred after consolidation therapy in which patients were assigned to maintenance therapy with lenalidomide or lenalidomide/prednisone. Three hundred eighty-nine patients enrolled in the study, and 256 were eligible for randomization to the consolidation phase. The median duration of follow-up was 52.0 months. For the entire study population, the median PFS was 24.2, 27.6, 37.6, and 31.5 months for patients receiving CRD with lenalidomide/prednisone maintenance therapy, CRD with lenalidomide maintenance therapy, HDM/ASCT with lenalidomide/prednisone maintenance therapy, and HDM/ASCT with lenalidomide maintenance therapy, respectively, whereas the 4-year OS was 68%, 76%, 77%, and 75% (*P* values not provided). For the 256 patients eligible for consolidation therapy, the median PFS was 28.6 months for those receiving CRD and 43.3 months for those receiving HDM/ASCT (HR for the first 24 months, 2.51; *P*<.0001), whereas the 4-year OS was 73% in the CRD group vs 86% in the HDM/ASCT group (HR, 2.40; *P*=.004). Notably, only 37.2% to 57% of patients assigned to lenalidomide-based consolidation therapy in the 2 studies underwent HDM/ASCT as part of second-line therapy. Although the reasons are not outlined in detail, the data would suggest that the opportunity to pursue HDM/ASCT could be lost when reserved for relapsed disease, be it the result of prior treatment toxicity, inability to recapture control of the disease, or patient preference. Thus, these pivotal studies reaffirmed the clinical benefit of HDM/ASCT in the context of lenalidomide-based induction therapy.

Although the results of the above studies point to a continued role for HDM/ASCT consolidation therapy, a significant number of patients did not complete induction therapy. Secondly, the induction therapy and nontransplant consolidation therapy did not contain a proteasome inhibitor, and we now know that combinations of proteasome inhibitors, immunomodulatory drugs, and corticosteroids are the optimal strategies for induction therapy and are capable of producing unprecedented depths of response.[13-16] It should be noted that when MPR was used without lenalidomide maintenance therapy, it was no better than either melphalan/prednisone (MP) or MP/thalidomide in newly diagnosed patients with multiple myeloma who were ineligible for transplant.[17,18]

More recent data from 2 ongoing studies have been presented and help clarify the role of HDM/ASCT in the context of bortezomib-based induction and consolidation therapy. The EMN02/HO95 MM study (A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone With High Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma) is a phase 3 trial in which patients were randomly assigned to early HDM/ASCT (either single or tandem HDM/ASCT, depending on the treatment center) vs four

42-day cycles of bortezomib, melphalan, and prednisone (VMP) consolidation after induction therapy with cyclophosphamide, bortezomib, and dexamethasone.[19] A second randomization was undertaken in which patients received consolidation therapy with lenalidomide, bortezomib, and dexamethasone or no consolidation therapy after HDM/ASCT or VMP. All patients received lenalidomide maintenance. The median follow-up from the first randomization was 24 months. An initial, prespecified interim analysis was performed after 33% of the required events had occurred. The rate of VGPR or better was higher in the HDM/ASCT arm than in the VMP arm (85.5% vs 73.8%; *P*<.001). Importantly, patients assigned to HDM/ASCT had a 24% reduction in the risk of disease progression or death, with a median PFS that had not been reached vs 44 months for those assigned to HDM/ASCT and VMP, respectively, and a 3-year PFS of 66.1% and 57.5% for those assigned to HDM/ASCT and VMP, respectively (HR, 0.73; *P*=.003). The improvement in PFS was seen for those with revised International Staging System (ISS) stage III disease (HR, 0.52; *P*=.008) and high-risk cytogenetics (t[4;14], del[17p], del[1p], gain 1q; HR, 0.72; *P*=.028). However, the difference in the 3-year PFS for those receiving VMP and single HDM/ASCT did not reach statistical significance (3-year PFS, 57.5% vs 63.0%, respectively; HR, 0.81; *P*=.06). Additionally, with early follow-up, the OS was similar between the HDM/ASCT and VMP arms.

One disadvantage of the EMN02/HO95 MM study is that it utilized induction therapy with cyclophosphamide, bortezomib, and dexamethasone, which has since been shown to produce a lower rate of high-quality responses compared with bortezomib, thalidomide, and dexamethasone.[20,21] The IFM/Dana Farber Cancer Institute (DFCI) 2009 trial is a randomized, phase 3 study evaluating early vs late HDM/ASCT in patients treated with induction therapy based on an immunomodulatory drug plus a proteasome inhibitor. After 3 cycles of lenalidomide, bortezomib, and dexamethasone (RVD) and subsequent stem cell collection, patients assigned to the delayed HDM/ASCT arm received an additional 5 cycles of RVD followed by lenalidomide maintenance therapy, whereas those in the early HDM/ASCT group went directly to HDM/ASCT, followed by 2 cycles of RVD consolidation therapy after HDM/ASCT and then lenalidomide maintenance therapy. Patients participating in the IFM portion of the study received 1 year of lenalidomide maintenance therapy, whereas participants in the United States received lenalidomide maintenance therapy until disease progression. Preliminary results from the IFM side of the study were presented at the 2015 American Society of Hematology Annual Meeting.[22] A total of 350 patients were assigned to the early-ASCT arm, and 350 patients were assigned to the delayed-ASCT arm. The median follow-up was 39 months. A second, prespecified interim analysis was performed after 69% of the required events had occurred, and the independent data management and safety committee recommended early termination of the trial owing to a PFS benefit seen with early HDM/ASCT. The rate of VGPR or better was 78% vs 88% (*P*=.001), the CR rate was 49% vs 59%, and the minimal residual disease (MRD) rate by multiparametric flow cytometry was 65% vs 80% (*P*=.001) for patients assigned to delayed vs early HDM/ASCT, respectively. Notably, the 3-year PFS was 48% vs 61%, the 4-year PFS was 35% vs 47%, and the median PFS was 34 months vs 43 months in favor of early HDM/ASCT (HR, 0.69; *P*<.001). A PFS benefit was seen regardless of ISS stage or the presence of standard-risk vs high-risk cytogenetics. Nonetheless, the 3-year OS was 88% for both arms, thus demonstrating excellent outcomes with both approaches. Results from the United States are eagerly anticipated and will clarify whether lenalidomide maintenance therapy used until disease progression will narrow the PFS difference between early and delayed HDM/ASCT approaches.

Carfilzomib, lenalidomide, and dexamethasone (KRD) therapy has been shown to be a highly effective induction strategy for the treatment of newly diagnosed multiple myeloma.[13] Thus, investigators from the Multiple Myeloma Research Consortium pursued a single-arm, phase 2 study evaluating HDM/ASCT as part of consolidation therapy for patients treated with KRD induction therapy.[23] Patients were treated with 4 cycles of KRD, HDM/ASCT, 4 cycles of KRD consolidation therapy, 10 cycles of KRD maintenance therapy, and subsequent lenalidomide monotherapy. Seventy-five patients were enrolled, 36% of whom had high-risk cytogenetics. Notably, the rate of VGPR or better increased from 77% to 98% from the end of induction therapy to the end of HDM/ASCT, whereas the rate of CR or better increased from 12% to 26% and the rate of stringent CR increased from 8% to 20%. By the end of KRD maintenance therapy, the rate of stringent CR was an unprecedented 82%. A similarly designed study in which patients received KRD without HDM/ASCT showed identical rates of stringent CR to the HDM/ASCT study at the end of induction therapy (8%). However, the HDM/ASCT study showed higher rates after consolidation therapy (68% vs 30%) and KRD maintenance (82% vs 51%). Although there may have been important differences in the makeup of the patient populations enrolled in the 2 studies (1 study was designed specifically for transplant-eligible patients, whereas the other was not), the data are provocative and clearly demonstrate incremental improvement in the

depth of response with the use of HDM/ASCT, even in patients treated with the best available triplet based on an immunomodulatory drug and a proteasome inhibitor.

Thus, whether used with an induction strategy based on lenalidomide, a proteasome inhibitor, or an immunomodulatory drug, HDM/ASCT consistently improves depth of response and PFS when used as consolidation therapy for multiple myeloma, and produces survival results previously unseen in phase 3 studies when utilized in first-line or second-line therapy. As such, high-dose therapy remains an important standard of care in multiple myeloma.

Autologous Stem Cell Transplant as Part of First-Line or Second-Line Therapy

In light of the advances in nontransplant therapy, the potential toxicities associated with HDM, and the increasing appreciation of the heterogeneous biology of multiple myeloma, the timing of HDM/ASCT in the therapy continuum for multiple myeloma is debated. Can some or all patients afford to defer HDM/ASCT until disease progression? As noted earlier, the lack of an OS advantage seen in some of the earlier phase 3 studies of CCT vs HDM/ASCT consolidation therapy was at least in part caused by the use of high-dose therapy at the time of disease progression. However, these studies were not designed to evaluate the optimal timing of HDM/ASCT consolidation therapy. The first phase 3 study directly addressing this issue was published in 1998 by Fermand and colleagues.[24] Patients were assigned to early or delayed high-dose therapy. All patients underwent stem cell collection at the beginning of the study. Seventy-four of 81 eligible patients in the delayed-HDM/ASCT arm underwent salvage HDM/ASCT at progression. Although the median EFS was 39 months in the early-HDM/ASCT arm compared with 13 months for those assigned to delayed HDM/ASCT, the median OS was 64.6 and 64.0 months, respectively (P=.92). An analysis of the average time without symptoms, treatment, and treatment toxicity (TWiSTT) was undertaken to determine if a more durable remission as a result of early HDM/ASCT would lead to a longer period that was free from treatment and its attendant side effects. Indeed, the average TWiSTT was 27.8 and 22.3 months for those assigned to early vs late HDM/ASCT. Although an improved treatment-free interval and freedom from therapy side effects are compelling rationales for pursuit of early HDM/ASCT, the applicability of this benefit is less clear in an era where the treatment paradigm is evolving into one of continuous therapy until disease progression rather than intermittent therapy of fixed duration.[25]

Although the Fermand study would suggest that HDM/ASCT can be performed as part of first-line or second-line therapy, the previously noted Palumbo and Gay studies demonstrated an OS advantage with early HDM/ASCT, at least for those patients who tolerated and responded to lenalidomide and dexamethasone induction therapy.[11,12] On the other hand, it remains unclear whether this is the case with the application of more effective induction and nontransplant consolidation therapy consisting of a proteasome inhibitor, a corticosteroid, and either an immunomodulatory drug or an alkylating agent. In this regard, early OS data from the EMN02/H095 and IFM/DFCI 2009 trials demonstrate equivalent survival outcomes between the early and deferred HDM/ASCT arms.[19,22] Moving forward, it will be critical to evaluate OS with longer follow-up and to capture the rate of HDM/ASCT performed at relapse for those assigned to delayed HDM/ASCT, as well as the reasons HDM/ASCT was not pursued when applicable. It will be important to determine if there are subgroups of patients who derive more benefit than others from an early approach (eg, patients with high-risk cytogenetics). Additionally, it will be interesting to see what proportion of patients assigned to delayed HDM/ASCT go into long-term remission with first-line therapy in the US portion of the IFM/DFCI 2009 study, and what the biologic makeup of their disease is. Ultimately, in addition to traditional clinical efficacy measures, important considerations when assessing the superiority of one approach over the other include the short- and long-term adverse effects of treatment, the impact of myeloma-related morbidity, patient-reported outcomes, and health care costs.

For now, given that the majority of published studies demonstrating the benefit of HDM/ASCT in multiple myeloma incorporated high-dose therapy as part of first-line treatment, the standard approach to a transplant-eligible, newly diagnosed patient with multiple myeloma treated outside of a clinical study should be early HDM/ASCT. Nonetheless, in light of the clear clinical benefit seen with the use of delayed HDM/ASCT, deferment of HDM/ASCT until second-line therapy is reasonable, especially for healthier, younger patients with lower-risk disease, who are more likely to remain good candidates for high-dose therapy at relapse (eg, revised ISS stage I disease).[26] Any decision to defer HDM/ASCT must be made with appropriate patient counseling, outlining the risks and benefits of the 2 approaches. When possible, stem cells should be collected after initial induction therapy to minimize the risk of unsuccessful mobilization at relapse. Lastly, patients who defer HDM/ASCT should be offered high-dose therapy for first relapse after a course of initial cytoreductive salvage therapy, given that there are no phase 3 studies demonstrating the value of an initial HDM/ASCT beyond second-line therapy.

Single vs Tandem Autologous Stem Cell Transplant

The feasibility, safety, and clinical efficacy of tandem HDM/ASCT was first studied in the 1980s.[27] Barlogie and colleagues at the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences further developed this approach, incorporating tandem HDM/ASCT into the framework of their Total Therapy treatment approaches and achieving durable complete responses for many of their patients.[28-31] To better understand the additional value of the second HDM/ASCT, Attal and coinvestigators conducted a phase 3 study comparing single HDM/ASCT (melphalan 140 mg/m^2 + total body irradiation) with tandem HDM/ASCT (ASCT 1: melphalan 140 mg/m^2; ASCT 2: melphalan 140 mg/m^2 + total body irradiation) in patients with newly diagnosed multiple myeloma who were younger than 60 years.[32] After induction therapy with 3 to 4 cycles of infusional vincristine and doxorubicin with pulse dexamethasone (VAD), 85% of patients assigned to single HDM/ASCT successfully underwent the planned high-dose therapy, whereas 88% of patients assigned to tandem HDM/ASCT underwent the first HDM/ASCT and 78% underwent the second HDM/ASCT. Twenty-two percent of those receiving single HDM/ASCT underwent transplant as salvage therapy at relapse, in contrast to 26% of those assigned to tandem HDM/ASCT. The median EFS for those assigned to single HDM/ASCT was 25 months, whereas the median EFS for the tandem HDM/ASCT group was 30 months (P=.03). The median OS was 48 months vs 58 months (P=.01), and the 7-year OS was 21% vs 42%, respectively. In subset analysis, patients who did not have at least a VGPR after the first HDM/ASCT benefitted the most from the second HDM/ASCT, with a 7-year OS of 43%, compared with 11% for those undergoing single HDM/ASCT. There was no survival advantage demonstrated for the patients who had at least a VGPR after their first HDM/ASCT.

A similar study was conducted by Cavo and colleagues, in which patients were randomly assigned to either single HDM/ASCT (melphalan 200 mg/m^2) or tandem HDM/ASCT (ASCT 1: melphalan 200 mg/m^2; ASCT 2: melphalan 120 mg/m^2 + busulfan 12 mg/kg) after an initial 4 cycles of VAD induction therapy.[33] Eighty-five percent of patients assigned to single HDM/ASCT successfully underwent the therapy, whereas 90% of those assigned to tandem HDM/ASCT received the first ASCT and 65% received the second ASCT. Thirty-three percent of those assigned to single HDM/ASCT underwent ASCT as a salvage therapy at relapse, in contrast to 10% of those undergoing tandem HDM/ASCT. As with the study by Attal and coinvestigators, the median EFS was improved for those assigned to the tandem HDM/ASCT arm of the study (35 months vs 23 months; P=.001). However, no OS advantage was demonstrated (median OS, 65 months vs 71 months; P=.90; 7-year OS, 46% vs 43%). Patients who did not achieve a near CR benefitted the most from a tandem HDM/ASCT strategy, achieving a median EFS of 42 months vs 22 months (P<.001) and a trend toward improved OS (7-year OS, 60% vs 47%; P=.10).

Unfortunately, the phase 3 studies comparing single to tandem HDM/ASCT were performed prior to the availability of the immunomodulatory drugs and proteasome inhibitors and the frequent use of consolidation and maintenance therapy after HDM/ASCT. As such, the relevance of these findings to current practice is not clear, particularly given the fact that a large majority of patients are now able to achieve at least a VGPR after initial induction therapy and single HDM/ASCT. Nonetheless, there may yet be a role for tandem HDM/ASCT in modern myeloma therapy. A retrospective analysis was performed on four phase 3 studies in which single or tandem HDM/ASCT therapy was pursued after bortezomib-based induction therapy.[34] The choice of single vs tandem HDM/ASCT was determined by the center at which the patient was treated. The median PFS was 38 vs 50 months for those receiving single or tandem HDM/ASCT, respectively (HR, 0.72; P<.001), whereas the 5-year OS was 63% vs 75% (P=.002). For those with high-risk cytogenetics (t[4;14] and/or del[17p]) who had not entered a CR with induction therapy, the median PFS was 42 vs 21 months (HR, 0.41; P=.006) and the 5-year OS was 70% vs 17% (HR, 0.22; P<.001) in favor of a tandem HDM/ASCT approach. Additionally, for the EMN02/HO95 MM study outlined earlier, the 3-year PFS for those who underwent tandem ASCT was 73.1%, compared with 63.0% for those receiving single HDM/ASCT (HR, 0.69; P=.03).[19]

To resolve the debate, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) undertook a prospective phase 3 study (NCT01109004; BMT CTN 0702; Stem Cell Transplant With Lenalidomide Maintenance in Patients With Multiple Myeloma) in which patients who had undergone initial induction therapy followed by single HDM/ASCT were assigned to 1 of 3 treatment arms: (1) a second HDM/ASCT followed by lenalidomide maintenance therapy; (2) 4 cycles of consolidation therapy after HDM/ASCT with lenalidomide, bortezomib, and dexamethasone followed by lenalidomide maintenance therapy; or (3) lenalidomide maintenance therapy alone. This study has completed enrollment and should help address whether a second HDM/ASCT is beneficial in the context of currently available induction therapies based on immunomodulatory drugs and proteasome

Table 2. Retrospective Analyses of Salvage High-Dose Melphalan Supported by Autologous Stem Cell Transplant in Relapsed Multiple Myeloma

Study	Results[a]	Factors Associated With PFS and OS
Cook,[45] 2011	- 4-y OS: 32% for HDM/ASCT, 22% for CCT - Median OS for patients with RD >18 mo: 3.9 y for HDM/ASCT, 1.8 y for CCT	- RD >18 mo, younger age associated with improved OS
Yhim,[40] 2013	- Median PFS: 18 mo for HDM/ASCT, 9.1 mo for CCT - Median OS: 55.5 mo for HDM/ASCT, 25.4 mo for CCT	- CCT, RD <18 mo, ISS stage III disease associated with worse OS
Fenk,[42] 2011	- Median EFS: 14 mo - Median OS: 52 mo	- RD >12 mo
Gonsalves,[41] 2013	- Median PFS: 10.3 mo, median OS: 33 mo - Median OS from relapse after ASCT 1: 57 mo for HDM/ASCT, 46 mo for CCT	- RD >12 mo, fewer lines of therapy, CR with ASCT 2 associated with better TTP - RD >12 mo associated with better OS
Jimenez-Zepeda,[39] 2012	- RD ≤24 mo - Median PFS: 9.83 mo, median OS: 28.47 mo - RD >24 mo - Median PFS: 17.3 mo, median OS: 71.3 mo	- RD >24 mo associated with improved PFS and OS
Lemieux,[38] 2013	- Median PFS: 18 mo - Median OS: 4 y	- Inferior PFS: RD <24 mo, <VGPR with salvage treatment, no maintenance therapy - Inferior OS: Age >60 y, RD <24 mo
Michaelis,[37] 2013	- Median PFS: 18 mo (3-y PFS: 13%) - 3-y OS: 46%	- RD ≥36 mo, 3-y OS: 58% - RD <36 mo, 3-y OS: 42%
Olin,[36] 2009	- Median PFS: 8.5 mo - Median OS: 20.7 mo	- RD ≤12 mo, ≥5 prior lines of therapy associated with worse OS
Shah,[35] 2012	- Median PFS: 12.3 mo - Median OS: 31.7 mo	- Shorter RD, ↑ number of prior lines of therapy associated with worse OS

ASCT, autologous stem cell transplant; ASCT 1, initial autologous stem cell transplant; ASCT 2, salvage autologous stem cell transplant; CCT, conventional chemotherapy; EFS, event-free survival; HDM, high-dose melphalan; ISS, International Staging System; mo, month/months; OS, overall survival; PFS, progression-free survival; RD, remission duration; TTP, time to progression; VGPR, very good partial response; y, year/years.

[a] RD, PFS, TTP, and OS measured from time of salvage ASCT.

inhibitors, and the widespread use of consolidation and maintenance therapy after HDM/ASCT. It is important to learn whether subsets of patients exist who benefit from a particular strategy, and whether consolidation or maintenance therapy after HDM/ASCT obviate the need for tandem HDM/ASCT. Until these data mature and are able to inform practice, it is advisable to collect enough stem cells for 2 ASCTs and consider a tandem HDM/ASCT strategy for high-risk patients who achieve further cytoreduction of disease with their initial HDM/ASCT without excessive toxicity.

The Role of Salvage Autologous Stem Cell Transplant in Multiple Myeloma

OS outcomes are similar regardless of whether high-dose therapy is used as part of first-line or second-line treatment. Salvage HDM/ASCT therefore remains a standard of care for HDM-naive patients with first disease progression. However, for patients whose disease progresses after an initial HDM/ASCT, the role of repeat HDM/ASCT as part of salvage therapy remains less clear. Numerous retrospective analyses have been published (Table 2),[35-43] and several conclusions can be drawn. First, salvage HDM/ASCT is feasible, with nonrelapse mortality rates that are acceptably low. Second, several factors consistently emerge that are predictive of outcomes with salvage HDM/ASCT. Specifically, a shorter PFS, measured from the time of the first HDM/ASCT, is universally associated with shorter PFS and OS with a second transplant in multivariate analysis. The American Society for Blood and Marrow Transplantation, the European Society for Blood and Marrow Transplantation, the BMT CTN, and the International Myeloma Working Group recently published consensus guidelines on the use of salvage HDM/ASCT in relapsed multiple myeloma.[44] There was strong consensus that patients with a remission duration of more than 24 months with their first HDM/ASCT should be offered a second HDM/ASCT, whereas those with a remission duration of less than 6 months

were less likely to derive clinical benefit. Opinion was more varied for those with remission durations of 12 to 24 months. Ultimately, consensus was reached that patients with a remission duration of more than 18 months should be considered for a second HDM/ASCT. In addition to remission duration with the first HDM/ASCT, another risk factor was an increased number of prior lines of therapy, which corresponded to a shorter PFS, and in some cases, shorter OS, after a second HDM/ASCT. These data suggest that a salvage HDM/ASCT should be considered earlier in the course of the treatment continuum and not in advanced disease refractory to all available therapies. Lastly, several studies revealed age to be a predictor of OS with salvage HDM/ASCT, thus indicating that frailer patients should not be considered for such an approach.

Although the above retrospective analyses are instructive, they are inherently limited by unaccounted variables that may influence the decision to pursue high-dose therapy vs CCT. Additionally, these studies did not account for potential differences in the therapy provided before or after HDM/ASCT (eg, post-ASCT consolidation and maintenance therapy). An 18-month remission after HDM/ASCT for a patient who did not receive any therapy after HDM/ASCT is certainly not the same as an 18-month remission in a patient who received 2 cycles of lenalidomide, bortezomib, and dexamethasone consolidation therapy followed by lenalidomide maintenance therapy. Lastly, a longer duration of remission with a first HDM/ASCT may be predictive of improved PFS and OS not only with salvage HDM/ASCT, but with nontransplant therapy as well. In this regard, Yhim and coinvestigators undertook a matched-pair analysis of salvage HDM/ASCT vs chemotherapy and found that patients with ISS stage I or II disease at diagnosis and a time to progression of more than 18 months from the first HDM/ASCT did equally well with chemotherapy or HDM/ASCT at relapse (median OS, 77.3 months vs 75.3 months, respectively; P=.919).[40]

Recognizing the limitations of the above retrospective analyses, Cook and colleagues undertook a phase 3 study comparing CCT at relapse with HDM/ASCT.[45] Patients with progressive disease at least 18 months from their initial HDM/ASCT (later reduced to 12 months) underwent initial cytoreductive therapy with 2 to 4 cycles of bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy followed by peripheral blood stem cell collection (if not already available). Ninety-four percent of registered patients were bortezomib-naive and none had received lenalidomide as part of first-line therapy. Patients with adequate stem cells for a second ASCT were randomly assigned to treatment with HDM (200 mg/m^2)/ASCT or cyclophosphamide (400 mg/m^2 once weekly for 12 weeks). Of the 293 patients who underwent PAD induction therapy, 174 had adequate numbers of stem cells to pursue a second ASCT. The rate of VGPR or better was 47% for patients assigned to cyclophosphamide and 60% for patients assigned to HDM/ASCT (P=.0036), and the rate of stringent CR was 22% vs 39% (P=.021). Importantly, the median time to progression was 11 months for those assigned to cyclophosphamide vs 19 months for those assigned to ASCT (HR, 0.36; P<.0001). In addition, the median time to progression was 11 months for those assigned to cyclophosphamide vs 24 months for those assigned to HDM/ASCT among those with a remission duration of more than 24 months with the first HDM/ASCT (HR, 0.35; P<.0001). For those with a remission duration after the initial HDM/ASCT of 12 to 24 months, the median time to progression was 9 months with cyclophosphamide and 13 months with HDM/ASCT (HR, 0.37; P<.0037). There was a trend towards better OS for those assigned to HDM/ASCT, with a 3-year OS of 62.9% for those assigned to cyclophosphamide vs 80.3% for those assigned to HDM/ASCT, but this did not reach statistical significance (HR, 0.62; P=.19). Although the results of this study are important, the sample size was small, and the comparator arm of weekly cyclophosphamide would not be considered a standard nontransplant salvage therapy in the current era of myeloma therapy.

Similarly designed phase 3 studies utilizing current treatment paradigms are crucial to better understand the role of a second HDM/ASCT in patients with relapsed multiple myeloma. For now, decisions should be made on a case-by-case basis, weighing the duration of response to the first HDM/ASCT, the application of consolidation and maintenance therapy after HDM/ASCT, and adverse events associated with the initial HDM/ASCT. Lastly, given the suboptimal remission durations seen when compared with early HDM/ASCT, salvage HDM/ASCT represents a fruitful platform for the study of novel conditioning strategies, as well as consolidation and maintenance therapies after HDM/ASCT that can subsequently be applied to ASCT-based, first-line therapy.

Conclusion

Outcomes have dramatically improved for the majority of patients with multiple myeloma. Although the debate will likely continue regarding the magnitude of benefit associated with the use of HDM/ASCT and the optimal timing of its use in modern myeloma therapy, published and ongoing studies clearly demonstrate that HDM/ASCT leads to improvements in depth of response and PFS in the context of the best currently available therapies. Additionally, regimens utilizing HDM/ASCT as part of first-

line or second-line therapy are producing unprecedented survival outcomes in ongoing phase 2 and 3 studies.

Moving forward, it will be critical to identify patient subsets who are more likely to benefit from early HDM/ASCT, as well as those who may not require such an approach at all. Detection of MRD by flow cytometry and next-generation sequencing has emerged as a powerful tool in the monitoring of response depth in multiple myeloma.[46-49] Future studies will need to address whether we can use MRD status as a basis for making decisions about ASCT-based therapy.

Additionally, as the use of induction therapy based on immunomodulatory drugs and proteasome inhibitors becomes more ubiquitous, a better understanding of the role of a repeat HDM/ASCT at disease progression will become more essential. It is important to remember that the use of aggressive, continuous treatment based on immunomodulatory drugs and proteasome inhibitors as part of early therapy may affect the performance of these regimens in the setting of relapsed or refractory disease.

Similarly, recommendations regarding the optimal candidates for a second HDM/ASCT will need to be updated and will increasingly account for the application of continuous therapy after first HDM/ASCT, be it consolidation therapy or maintenance therapy. Novel conditioning and post-ASCT consolidation and maintenance strategies will need to be studied if salvage HDM/ASCT is to remain a viable therapeutic option in the future. Lastly, it will be important to continually reassess the place of HDM/ASCT as monoclonal antibodies are incorporated into existing induction therapies—with the use of immunomodulatory drugs and proteasome inhibitors—and the area of immunotherapy emerges in multiple myeloma. Indeed, the advent of immune checkpoint inhibitors, new monoclonal antibodies, antibody-drug conjugates, and chimeric antigen receptor T-cell therapy mandates that we continually challenge established treatment paradigms. Will these emerging therapies simply be incorporated into a continuum of myeloma therapy that includes HDM/ASCT, or will they eventually obviate the need for high-dose therapy? Certainly, continued pursuit of rigorous, collaborative phase 3 studies to help answer these questions in real time will be critical if we are to further advance patient outcomes.

Disclosures

Dr Voorhees has consulted for Celgene, Millennium Takeda, Bristol-Myers Squibb, Novartis, Array BioPharma, and Janssen; and has received research funding from GSK, Janssen, Merck, Amgen, Oncopeptides, and Acetylon. Dr Usmani has consulted for Celgene, Millennium Takeda, Onyx, and Sanofi; has received speaker's fees from Celgene, Millennium Takeda, and Onyx; and has received research funding from Array BioPharma, Celgene, Janssen, Onyx, Pharmacyclics, and Sanofi.

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Erratum

An article in the July 2016 issue, "Bruton's tyrosine kinase inhibitors in chronic lymphocytic leukemia and lymphoma" by Gaurav Varma, MSPH, Tyler P. Johnson, MD, and Ranjana H. Advani, MD, described ONO/GS-4059 as a "reversible" inhibitor of BTK when it is in fact an "irreversible" inhibitor. We have made the correction to pages 546 and 552 of the online version at www.hematologyandoncology.net. Many thanks to an astute reader for pointing out the error.