Delaying the Use of High-Dose Melphalan With Stem Cell Rescue in Multiple Myeloma Is Ready for Prime Time

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Abstract: The significant advances made in the treatment of multiple myeloma (MM) have allowed for a paradigm shift away from the early use of high-dose melphalan with autologous stem cell transplant (HDM-ASCT). In 2015 alone, the US Food and Drug Administration (FDA) approved 4 novel drugs for MM. Novel drugs and regimens have shown unprecedented efficacy, which has increased the tempo of new drug development. Furthermore, the FDA recently approved a diagnostic test to detect minimal residual disease (MRD) that will allow community clinicians to conduct real-time testing of MRD. Most importantly, frontline regimens based on immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) have shown a large clinical benefit. The next era has begun, as several 4-drug combinations that include monoclonal antibodies are being evaluated in clinical trials in the attempt to replace HDM-ASCT in the treatment of MM. We and others have therefore questioned the need for early HDM-ASCT, especially in light of the possible complications. HDM-ASCT is associated not only with acute toxicities—cytopenia, infection, and even death—but also an increased risk of developing secondary cancers. This article discusses the historic context of HDM-ASCT, the modern role of HDM-ASCT given the availability of highly sensitive MRD testing, and the likely future of quadruplet treatment. In summary, patients who attain deep responses using IMiD- and PI-based regimens may not require early HDM-ASCT. A delayed approach to this treatment is acceptable, and might be preferred by patients.

Introduction

Multiple myeloma (MM) is a neoplastic disorder that is characterized by clonal proliferation of plasma cells. The cell of origin is from the post-germinal lymphoid B-cell lineage after lineage commitment in the bone marrow of progenitor cells.[1,2] The plasma cell disorders cross a spectrum of diseases, from premalignant plasma cell proliferation (monoclonal gammopathy of undetermined significance and smoldering MM), which is asymptomatic, to malignant disease (MM and

plasma cell leukemia), which produces end-organ damage and is associated with patient morbidity.[3,4] All cases of MM are preceded by a precursor stage known as monoclonal gammopathy of undetermined significance.[5,6] MM accounts for 1% of all cancers and is the second most common hematologic malignancy after lymphoma, with an estimated 32,110 new cases and 12,960 deaths in the United States occurring in 2019.[7-10] MM is a disease of the elderly, with a median age of diagnosis of approximately 66 to 70 years; only 37% of patients are younger than 65 years at diagnosis. It is extremely rare in people younger than 30 years (<0.5%).[4,10,11] MM occurs more commonly in blacks than in whites, and is slightly more common in men than in women.[10]

Historical Context of MM Treatment

The current tempo of drug development in MM has been encouraging to patients as well as to other stakeholders. Prior to approximately 2005, the prognosis in MM was dismal because of the unavailability of novel effective therapies and the lack of widespread use of high-dose melphalan with autologous stem cell transplant (HDM-ASCT). It was in the mid-1980s that Barlogie and others pioneered the use of HDM-ASCT for MM.[12] Initially, in a study of 23 patients with advanced relapsed/refractory MM (RRMM), HDM-ASCT was of limited benefit and sometimes led to early death. However, by the mid-1990s, the Intergroupe Francophone du Myélome (IFM) showed benefit from HDM-ASCT in a randomized study of patients with newly diagnosed MM (NDMM).[13] In this study, patients were randomly assigned to HDM-ASCT or conventional chemotherapy with alternating cycles of vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) and carmustine, vincristine, doxorubicin, and prednisone (BVAP). The median event-free survival (EFS) and overall survival (OS) in the conventional-dose group were 18 months and 37.4 months, respectively, vs 27 months and not reached in the HDM-ASCT group. Importantly, this study demonstrated the significantly inferior outcomes (ie, median OS ~3 years) with conventional chemotherapy compared with modern-day novel regimens. Figure 1 shows the relative improvements with older and novel regimens.

The last decade has been associated with significant advances in MM drug development and subsequent US Food and Drug Administration (FDA) approvals of novel therapeutics.[14] These advances have translated not only to unprecedented overall response rates (ORRs) but also to improvements in the longer-term endpoints of progression-free survival (PFS) and OS. This is most evidenced by the doubling of median survival rates from the 1980s to the 2010s.[1] Prior to the use of novel regimens, treatment with available traditional cytotoxic chemotherapeutics was associated with only modest benefit and significant morbidity and mortality. The current improvement in the natural history of MM can for the most part be attributed to the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). In the coming decade, the introduction of newer-generation PIs, IMiDs, and monoclonal antibodies to our treatment toolbox and the addition of monoclonal antibodies to triplet backbones will likely lead to further improvements in clinical outcomes. Several combinations are currently being evaluated in ongoing registrational studies.

Given the unprecedented activity and relative safety of these new regimens, the role of early HDM-ASCT for every patient is being reevaluated. HDM-ASCT can cause multiple immediate toxicities and long-term complications, including infections and death.[15] In countries where patients have access to modern MM drugs, the current gold standard of treatment is triplet combinations based on IMiDs and PIs. Triplet regimens have shown improved PFS and OS compared with doublet regimens, in both NDMM and RRMM.[14,16,17] With this, it is becoming more and more apparent that HDM-ASCT should not be considered mandatory for every patient, but rather tailored based on up-front depth of response with novel combination therapy.

We recommend giving 4 to 6 cycles of combination therapy followed by stem cell harvest for eligible patients. In cases where minimal residual disease (MRD) negativity is not attained, we continue with 2 to 4 more cycles of combination therapy, offer HDM-ASCT if MRD positivity persists, and then administer continuous maintenance therapy. Both prospective and retrospective studies have demonstrated the clinical benefit of continuous maintenance therapy.[18-24]

Modern Novel Combination Regimens for the Treatment of NDMM

The following IMiD- and PI-based combinations are the current gold standard in treating NDMM. The bortezomib (Velcade, Millennium/Takeda Oncology), lenalidomide (Revlimid, Celgene), and dexamethasone (VRd) regimen has been evaluated in pivotal phase 3 clinical studies.[25,26] Lenalidomide, a second-generation IMiD, is a thalidomide analogue, whereas the first-generation PI bortezomib targets the 20S subunit of the proteasome. The SWOG S0777 trial (Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma) randomly assigned patients to receive either VRd or Rd. The ORR and the complete response (CR) rate in the VRd arm were 82% and 16%, respectively. The median PFS

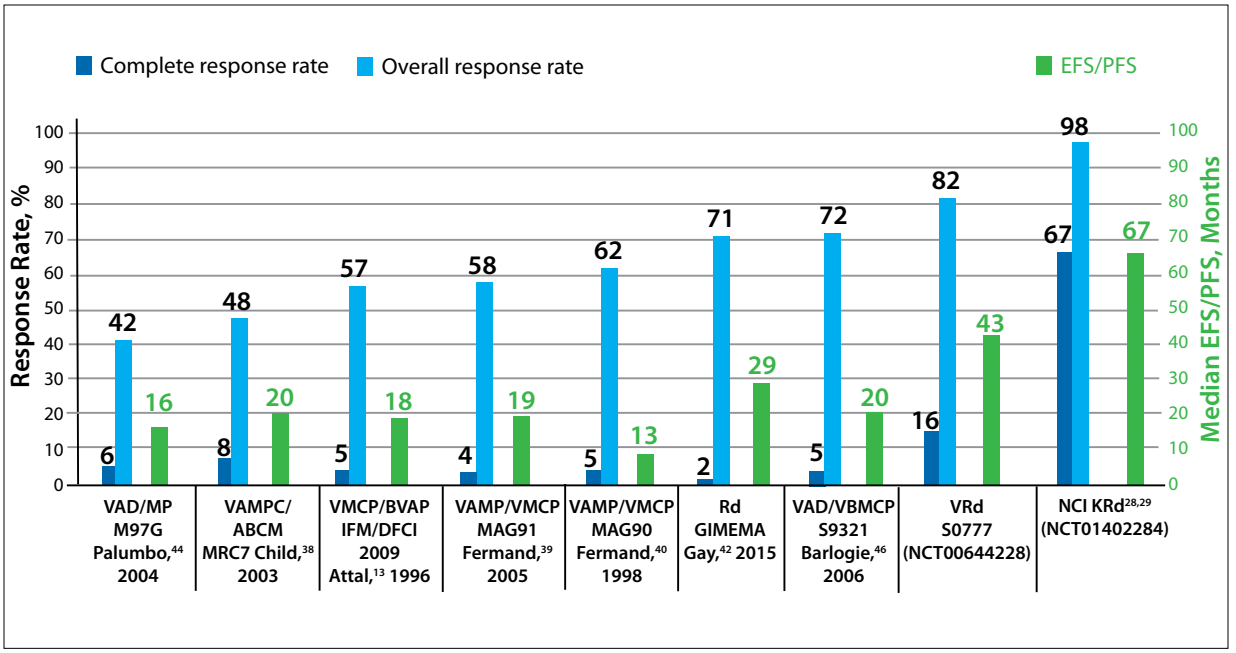

Figure 1. Activity of prenovel and novel regimens.

ABCM, doxorubicin, carmustine, cyclophosphamide, and melphalan; BVAP, carmustine, vincristine, doxorubicin, and prednisone; EFS, event-free survival; GIMEMA, Gruppo Italiano Malattie Ematologiche; KRd, carfilzomib, lenalidomide, and dexamethasone; IFM/DFCI, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MP, melphalan and prednisone; NCI, National Cancer Institute; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; VAMP, vincristine, doxorubicin, and methylprednisolone; VAMPC, vincristine, doxorubicin, methylprednisolone, and cyclophosphamide; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VMCP, vincristine, melphalan, cyclophosphamide, and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone.

was 43 months and the median OS was 75 months.[16] The VRd-only arm of the IFM/DFCI 2009 study (Study Comparing Conventional Dose Combination RVD to High-Dose Treatment With ASCT in the Initial Management of Myeloma in Patients Up to 65 Years) was associated with an ORR of 97%, a CR rate of 48%, and median PFS of 36 months.[27] Much like bortezomib, the second-generation PI carfilzomib (Kyprolis, Amgen) selectively targets the chymotrypsin activity of the 20S proteasome subunit (causing less peripheral neuropathy than bortezomib) and is used in combination with lenalidomide and dexamethasone.[14,28-31] In the phase 2 National Cancer Institute (NCI) study of carfilzomib, lenalidomide, and dexamethasone (KRd), which incorporated 2 years of lenalidomide maintenance without early HDM-ASCT, the ORR was 98%, with a median duration of response of 66 months.[28,29,32] Moreover, 62% of patients attained MRD negativity (10^{-5} sensitivity), with a median duration of more than 52 months. The median time to progression was 67 months and at a 6-year milestone, the probability of survival was 84.3%. Patients who attained MRD negativity by the end of cycle 8 had a 78% reduction in risk of progression. Similar efficacy results for carfilzomib-based combinations and the ability of carfilzomib to overcome poor cytogenetic risk have also been reported in other studies.[33-37]

Role of HDM-ASCT in NDMM in the Era of Novel Regimens

In the era of novel therapeutics, the question of whether HDM-ASCT is required for every patient is raised. To date, the IFM/DFCI 2009 study is the only reported study that has attempted to answer this question using a PI/IMiD-based triplet combination. Supporters of early HDM-ASCT who state that early HDM-ASCT is associated with improved survival use as reference clinical studies that do not incorporate novel triplet IMiD/PI-based combinations prior to high-dose melphalan. The majority of studies have used older toxic and inferior cytotoxic combinations, including VMCP, BVAP, and other similar regimens.[13,38-40] Figure 1 clearly shows the modest benefit of these earlier regimens compared with VRd or KRd. Not surprisingly, the IFM/DFCI 2009 study has thus far failed to show an OS benefit with early HDM-ASCT.[27] Although HDM-ASCT was associated with improved

PFS, it is of limited clinical benefit because of its toxicity. Moreover, patients who attained MRD-negative responses did not appear to benefit from early HDM-ASCT in terms of either PFS or OS. For these reasons, we believe that the benefit/risk balance and HDM-ASCT paradigm has changed, and that not every patient requires HDM-ASCT—although some will require it despite receiving an IMiD- and PI-based combination. The use of early HDM-ASCT should be discussed with the individual patient in the light of significant toxicity balanced only by a PFS benefit.[41]

The toxicity and morbidity associated with HDM-ASCT are not trivial. Acute toxicities include prolonged bone marrow suppression, infection, sepsis, veno-occlusive disease, interstitial pneumonitis, graft-versus-host disease, and graft failure. Although adverse reactions have been poorly captured and reported in historical HDM-ASCT MM trials,[13,20,27,38-40,42-46] acute grade 3/4 toxicities in these trials included neutropenia (80%-94%), thrombocytopenia (82%-94%), gastrointestinal disorders (9%-65%), and infections (16%-44%). Moreover, early treatment-related death occurred in up to 10% of patients. Furthermore, in a 2012 Cochrane review, the authors reported that no quality-of-life (QOL) or other patient-reported outcome (PRO) data were available for any of the 14 controlled studies. Owing to poor publication presentation and inconsistent definitions, treatment-related toxicity and death could not be evaluated.[47] More recently, PRO results were reported for the Myeloma X trial (High-Dose Melphalan and a Second Stem Cell Transplant or Low-Dose Cyclophosphamide in Treating Patients With Relapsed Multiple Myeloma After Chemotherapy) evaluating salvage ASCT in RRMM. The authors found that patients undergoing ASCT had a reduction in QOL and greater impact from treatment-related toxicity that lasted for 6 months, as well as higher scores for pain interference with daily living persisting up to 2 years.[48]

Significant long-term toxicity with HDM-ASCT includes cataracts, infertility, and an increased risk of secondary cancers, especially acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). A recent report that compared Surveillance, Epidemiology, and End Results (SEER) data with Center for International Blood and Marrow Transplant Research (CIBMTR) data found that the risk for both AML and MDS in Hodgkin lymphoma, non-Hodgkin lymphoma, and MM was 5 to 10 times higher the background rate in SEER data. The CIBMTR data representing only the HDM-ASCT–treated population showed a relative risk of 10 to 50 times higher than the background rate for AML and 100 times for MDS.[15] The risk of secondary malignancies is especially important given that patients with MM have nearly tripled their life expectancy with the introduction of modern therapies. The same patterns have occurred in breast cancer and other cancers treated with traditional therapies.[49-51]

Advancements in the Detection of Residual Disease

In parallel to drug development in MM, significant technical advancements in detection of occult or residual disease have been made. Traditionally, MM was diagnosed and monitored by older techniques of serum protein electrophoresis and imaging was performed with skeletal surveys (plain x-rays of the skull and long bones). However, the inferiority and inadequacy of these modalities have been shown more recently. In terms of residual disease, flow cytometry has been evaluated for the detection of disease that is not otherwise detectable. The original clinical studies incorporating flow cytometry to assess response used 4- and 6-color multiparametric flow cytometry technology.[52-54] Most importantly, these shed light on the importance of MRD testing, given that MRD negativity was a better predictor of long-term prognosis than traditional CR. The current gold standard in assessing MRD requires a sensitivity of at least 10^{-5}, which can be achieved only with more-advanced flow cytometry techniques incorporating at least 8-color flow technologies, according to the International Myeloma Working Group (IMWG) consensus criteria.[55] The NCI, Memorial Sloan Kettering Cancer Center (MSKCC), and EuroFlow consortium, along with other groups, have developed the required technologies, which incorporate 2-tube, 8-color and 1-tube, 10-color flow techniques.[56-58] This requirement is inherently a clinical practice limitation, given that clinical laboratories outside of dedicated cancer centers do not have this ability, and cross-center standardization is lacking in the United States. For example, in a survey of 30 major medical institutions in the United States, of which 11 responded, consistent flow panels were not used and most did not capture the required events or have the adequate number of aberrant cells to determine MRD.[59] Furthermore, fresh bone marrow aspirate samples are required for analysis, practically precluding the use of a standardized central reference laboratory.

In parallel to the advancement of flow cytometry techniques, next-generation sequencing (NGS) methods for identifying the unique plasma cell clone's V(D)J sequence have been developed and have improved sensitivity to 10^{-6}. Several companies have developed these assays, which are being used as laboratory-developed tests at a few institutions. For example, Adaptive Biotechnologies' clonoSEQ NGS assay received FDA approval for measur-

Table. Selected Studies of MRD Testing in Patients With Multiple Myeloma

Study	Treatment Arms	Test Method	Outcomes (MRD-Negative vs MRD-Positive)
Paiva,[78] 2008	6 alternating cycles of VBMCP and VBAD, followed by HDM-ASCT (n=577)	4-color flow cytometry	Median PFS 71 mo vs 37 mo (P<.001) Median OS not reached vs 89 mo (P=.02)
Paiva,[79] 2011	6 cycles of VMP or VTP (n=102)	4-color flow cytometry	Median PFS not reached vs 35 mo (P=.02) Median OS not significantly different
Korthals,[80] 2012	Idarubicin or dexamethasone plus HDM-ASCT (n=53)	ASO-PCR	Median EFS 35 mo vs 20 mo (P=.001) Median OS 70 mo vs 45 mo (P=.04)
Rawstron,[81] 2013	CVAD or CTD plus HDM-ASCT (n=378)	6-color flow cytometry	Median PFS 28.6 mo vs 15.15 mo (P<.001) Median OS 80.6 mo vs 59 mo (P=.018)
Puig,[82] 2014	VBMCP or VBAD induction therapy plus HDM-ASCT or 6 cycles of VMP or VTP (n=170)	ASO-PCR	VBMCP or VBAD induction therapy plus HDM-ASCT: median PFS 54 mo vs 27 mo (P=.001); OS not significantly different 6 cycles of VMP or VTP: median PFS not reached vs 31 mo (P=.029); OS not significantly different
Martinez-Lopez,[83] 2014	VBMCP or VBAD induction therapy plus HDM-ASCT or 6 cycles of VMP or VTP (n=133)	Next-generation V(D)J sequencing	Median time to progression 80 mo vs 31 mo (P<.0001) Median OS not reached vs 81 mo (P=.02)

ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVAD, cyclophosphamide, vincristine, daunorubicin, and dexamethasone; EFS, event-free survival; HDM-ASCT, high-dose therapy with melphalan and autologous stem cell transplant; mo, months; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; VBAD, vincristine, carmustine, daunorubicin, and dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VMP, bortezomib, melphalan, and prednisone; VTP, bortezomib, thalidomide, and prednisone.

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ing MRD in MM, which allows clinicians to send patient samples to their central laboratory for analysis. Along these lines, Invivoscribe has developed the LymphoTrack assay for in-house use as a laboratory-developed test. MSKCC and other institutions have used this technology to develop an MRD assay.[60] Not only does this technology have high analytic sensitivity, but samples do not have to be fresh, which allows for centralized laboratory testing. Limitations of this method include requirement of a baseline sample to determine the clonotype (eg, clonal V[D]J sequence) that, once known, can be followed for MRD. Also, in approximately 10% to 20% of cases, the baseline clonality cannot be determined. Advancements are being made, however, including the sequencing of the light chain locus to improve capture).[60]

Other methods have also been developed, such as allele-specific oligonucleotide polymerase chain reaction, but in general they are not practical for routine clinical use.[61] The Table shows some of the selected early studies incorporating MRD assessment. Moreover, radiographic techniques have also improved to detect occult disease, which the current IMWG response and MRD assessment criteria integrate.[55] The 2 main emerging imaging technologies used in MM are ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and diffusion-weighted magnetic resonance imaging (MRI). Both of these modalities are appealing compared with standard skeletal survey or CT because they detect actual myeloma deposits in both cortical and trabecular bone, as opposed to relying on the detection of bone destruction.[62] Much work has been done using these techniques, which should be incorporated into routine clinical practice. Furthermore, guidelines for imaging protocols are arising that will lead to standardization and the ability to compare scans across centers. Guidelines for acquiring, interpreting, and reporting whole-body MRI scans in myeloma, known as the Myeloma Response Assessment and Diagnosis System (MY-RADS), were recently published.[62] Nevertheless, the biggest obstacle to MRD assessment is the inability to have the required sensitivity using peripheral blood samples. In recent years, technologies evaluating both circulating tumor cells and circulating tumor DNA have been advanced in order to perform "liquid biopsies" in solid tumors. To date, however, the number of circulating tumor cells and the amount of circulating tumor DNA are insufficient to detect MRD in MM.

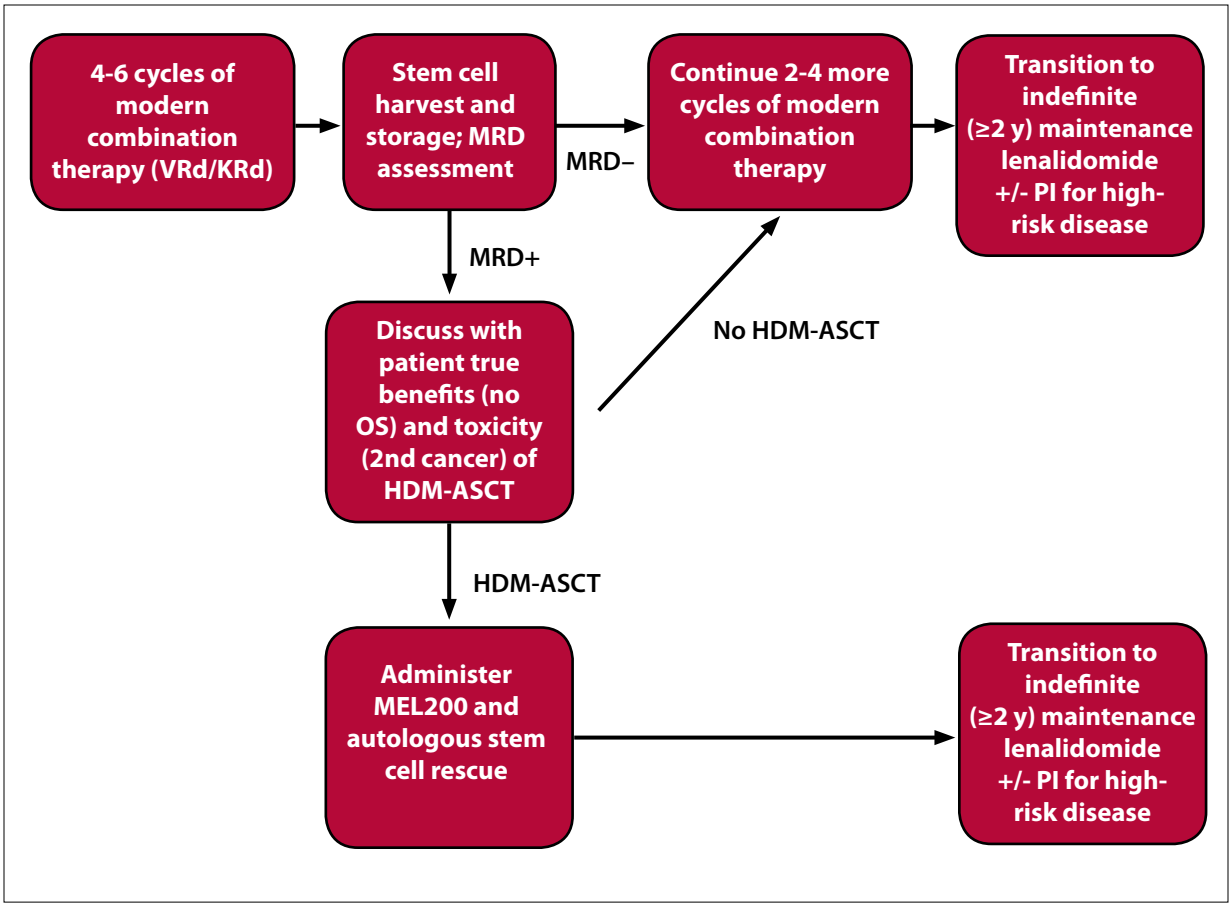

Figure 2. Practical treatment algorithm for transplant-eligible multiple myeloma.

HDM-ASCT, high-dose melphalan with autologous stem cell transplant; KRd, carfilzomib, lenalidomide, and dexamethasone; MEL200, melphalan 200 mg/m^2; MRD, minimal residual disease; OS, overall survival; PI, proteasome inhibitor; VRd, bortezomib, lenalidomide, and dexamethasone.

MRD Is the Most Important Prognostic Indicator

Development of techniques used to detect MRD with greater sensitivity (10^{-5} to 10^{-6}) has been critical in the field because newer therapies achieve deeper responses that traditional response criteria cannot detect.[63] MRD negativity as a marker of long-term clinical benefit has been established by 2 independent studies.[64,65] For example, MRD negativity was associated with a 65% reduction in the risk of disease progression or death (hazard ratio [HR], 0.35; *P*<.001) and a 52% reduction in the risk of death (HR, 0.48; *P*<.001). MRD assessment at a sensitivity of 10^{-5} or less (per IMWG guidelines) plays an important role in determining the use of HDM-ASCT.[55] In the IFM/DFCI 2009 study evaluating VRd with or without HDM-ASCT, MRD negativity was associated with a 78% reduction in the risk of progression or death (HR, 0.22; *P*<.01) and a 76% reduction in the risk of death (HR, 0.24; *P*=.001), regardless of HDM-ASCT, cytogenetic risk, or International Staging System (ISS) stage.[66] Similarly, in the single-arm NCI KRd study, patients who attained MRD negativity had a 78% reduction in the risk of progression (*P*=.005).[29]

The Role of MRD Testing and Who Should Receive HDM-ASCT

Given all of the above, early up-front HDM-ASCT is not blindly mandatory for every patient in current myeloma practice, but is needed for some. Patients who have attained MRD negativity in the context of highly active IMiD- and PI-based combination regimens are unlikely to derive benefit from early HDM-ASCT in terms of survival, and may experience only unneeded toxicity. The best example of this to date is the IFM/

DFCI 2009 study.[27] Figure 2 outlines a practical algorithm for clinicians.

In the coming decade, we will be able to characterize the true utility of MRD in a statistically prespecified and prospective fashion. For example, a phase 1/2 study evaluating combination therapy with KRd (NCT02937571) in NDMM integrates MRD testing into clinical decision-making to determine the ideal number of combination therapy cycles, based on MRD negativity.[67] Potential prospective trial designs using MRD testing to direct treatment with HDM-ASCT have been described.

Preliminary results were presented at the American Society of Clinical Oncology (ASCO) 2019 annual meeting on the FORTE study (Evaluation of the Safety and the Efficacy of Carfilzomib Combined With Cyclophosphamide and Dexamethasone or Lenalidomide and Dex Followed by ASCT or 12 Cycles of Carfilzomib Combined With Dex and Len for Patients Eligible for ASCT With Newly Diagnosed Multiple Myeloma), which evaluated KRd with and without HDM-ASCT.[68] Interestingly, no difference was seen in the depth (CR/MRD negativity) or frequency (ORR) of response between arms. Early data suggested that patients receiving HDM-ASCT might have a longer relapse-free survival, but it is too early to make solid conclusions.

Discussion

In modern-day treatment of NDMM with novel combination therapy, the use of early HDM-ASCT should not be mandated for every patient because a subset does not need it. The use of HDM-ASCT for the treatment of MM has been a significant development, but as we proceed to a new decade of advancements in both therapeutics and monitoring tools, the risk-to-benefit ratio of HDM-ASCT must be critically evaluated on an individual basis. With the availability of highly active combination therapy (eg, KRd) and the association of MRD negativity with improved survival, early HDM-ASCT is not mandatory for all patients with NDMM. Any potential benefit must be weighed against the real and potentially serious toxicities associated with HDM-ASCT. Based on the patient's response to combination therapy, his or her stem cells can be harvested and stored in case they are needed for rescue after HDM. In this fashion, a subset of patients, especially those who are MRD negative, can be spared the acute and long-term toxicities, including secondary cancers, associated with HDM-ASCT.

The CIBMTR study shows that the relative risk of developing AML/MDS is approximately 50 times higher in those with MM than in the general population. The overall 10-year absolute risk of secondary malignancies ranges from 11% to 16%, which many physicians argue is still very low.[69,70] However, given the fact that an increasing proportion of patients with MM are living longer, it will be important for the field to monitor the rates in patients for at least 10 after HDM-ASCT. Furthermore, a stable rate of 11% to 16% among long-term survivors will translate into higher overall numbers of secondary malignancies, as more patients live with the disease. More than 120,000 people are living with MM in the United States in 2019, and the prevalence continues to increase owing to longer survival driven by newer drugs. Secondary primary malignancies will most likely become a focus of MM research in the future.

Many groups have recently published guidelines and statements saying that given the superior MRD negative rates with modern therapy, a delayed approach is a perfectly acceptable alternative to early HDM-ASCT.[41,71-73] These various authors conclude that given the lack of a survival advantage with early HDM-ASCT, a delayed strategy is an acceptable approach based on patient-physician discussion. We fully agree with this recommendation. For example, in the recently published guidelines from ASCO/Cancer Care Ontario, the authors clearly state with recommendation 2.2 that "Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients." In addition, recommendation 7.6, which concerns relapse with no prior transplant, states that "After initial chemotherapy and collection of stem cells, patients can either proceed to early (up-front) ASCT or can opt for delayed ASCT at the time of relapse."[74] We believe that patients who achieve MRD negativity are those "select patients." This review article presents data suggesting that not only is a delayed approach to HDM-ASCT acceptable, it should be preferred in a subset of patients given the long-term consequences. We believe that the current level of evidence supports the selection of patients for an early vs delayed approach based on MRD negativity. We argue that VRd- and KRd-based combination therapy leading to MRD negativity neutralizes the potential long-term clinical benefit derived from early HDM-ASCT. We and others have shown that MRD negativity is a stronger predictor of long-term benefit than even age or cytogenetic risk.[29,75]

Summary of Recommendations

In summary, we recommend treatment of patients with NDMM using frontline combination therapy (KRd or VRd) for 4 to 6 cycles, followed by a stem cell collection. Based on the depth of response and MRD negativity at the time of stem cell collection, patients should be offered the option of forgoing early HDM-ASCT in favor of maintenance therapy until toxicity or progression. After

stem cell collection, 2 to 4 more cycles of combination therapy followed by maintenance therapy should be considered for patients who continue to respond to combination therapy but have not yet reached MRD negativity, although prospective studies are needed to determine the optimal number of cycles. As with all therapies, a careful assessment of risks vs benefits must be conducted prior to administration of additional cycles of therapy. In our experience with NDMM, patients reach MRD negativity after an average of 6 cycles of KRd.[28,29] In the near future, this paradigm may change to include monoclonal antibodies for a quadruplet combination, much like when rituximab was added to the cyclophosphamide, daunorubicin, vincristine, and prednisolone (CHOP) regimen for non-Hodgkin lymphoma.[76]

The purpose of this review article was to dissect available data and provide specialist interpretation on a current controversial topic in MM care. Many patients are asking questions related to the role of modern therapies, the use of novel methods for MRD tracking, and the true need for HDM-ASCT in the current era. Based on these facts, we were motivated to review and discuss current evidence. In this context, we recognize and respect that many nuances exist in every data set, and also that the exact interpretation of data varies among experts. This paper was written based on our review of available data and our clinical experience.

Administering HDM followed by stem cell infusions for faster recovery from chemotherapy has emerged as a subspecialty in the MM field since its introduction in the late 1980s.[77] Indeed, many of the current MM specialists around the world are trained in ASCT. Consequently, many institutions are set up to treat MM patients with HDM-ASCT. An extensive infrastructure has been built to treat and monitor patients with HDM-ASCT. It seems reasonable to believe that these doctors and institutions will not lead the MM field away from HDM-ASCT in favor of newer treatments integrated with MRD testing. Furthermore, in most countries outside the United States, access to newer MM drugs is restricted, and HDM-ASCT remains one of the most effective treatment options. Again, it seems reasonable to believe that such countries will not lead the myeloma field away from HDM-ASCT in favor of newer treatments integrated with MRD testing.

As with most other areas of medicine, early and late adopters of new treatment approaches will always exist. In fact, a range of opinions and variations in openness to novel ideas are to be expected. As we discussed in detail in this review article, the shift away from early HDM-ASCT for every patient to newer treatments integrated with MRD testing has already begun in the MM field. Data support the concept that MRD negativity itself is more important than the therapy used to achieve MRD negativity.[54,63,65] The main barriers preventing this change from occurring more quickly and across institutions/countries include inadequate access to modern therapies and validated MRD assays, resistance to change in treatment, and inadequate infrastructure. In our opinion, the use of delayed HDM with stem cell rescue in MM is ready for prime time in the United States and other countries with access to modern therapy, as long as the individual physician is ready.

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