blood® Review Series

ADVANCES IN MULTIPLE MYELOMA

Pros and cons of frontline autologous transplant in multiple myeloma: the debate over timing

Shaji K. Kumar, Francis K. Buadi, and S. Vincent Rajkumar

Mayo Clinic, Rochester, MN

The treatment landscape for multiple myeloma has dramatically changed over the past decade with the introduction of several new classes of drugs, which are very effective at controlling the disease for prolonged periods of time, especially when used in multidrug combinations. Prior to the advent of these new agents, peripheral blood autologous stem cell transplantation (ASCT) was the mainstay of therapy for patients who were eligible to undergo the procedure, with deep and durable responses in the majority of patients. Despite the introduction of more effective therapies, ASCT continues to play an important role in overall management of younger patients, where it has been integrated with the other therapeutic approaches to provide maximum benefit. Recent phase 3 trials have once again confirmed the survival benefit associated with ASCT in myeloma. Retrospective studies have also demonstrated the feasibility of using ASCT at the time of first relapse rather than as a component of the initial treatment. Significant geographical variations exist in the use of ASCT, especially between the United States and Europe in terms of its use as part of upfront therapy. Much of these differences are driven by the availability of drugs and drug combinations for initial therapy of myeloma as well as maintenance approaches post-ASCT. It is amply clear from these trials that ASCT will continue to play an important role in management of myeloma and is likely to be used as a platform for enhancing the efficacy of other treatment modalities that are currently in development. (*Blood*. 2019;133(7):652-659)

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy, and involves the post–germinal center, differentiated plasma cells.[1,2] It is a disorder of the older patient with a median age of 67-69 years in different studies.[3] During the past 2 decades, the outcomes of patients with myeloma has significantly improved with median survival going from 2 to 3 years at the turn of the century to 8 to 10 years based on the latest estimates from larger medical centers and phase 3 clinical trials.[4,5] A variety of reasons account for this progress including but not limited to better understanding of the disease biology, new more effective classes of drugs, increasing use of autologous stem cell transplantation (ASCT) in patients eligible to undergo the process, and more timely and effective management of disease complications, especially at the time of initial diagnosis.[6] ASCT likely represents the first major improvement in MM therapy since the introduction of melphalan and prednisone and its importance is highlighted by the early and more striking survival improvements observed among the younger patients.[7,8] However, it also remains the most debated therapy for myeloma, especially since the introduction of the newer drugs and their combinations, which are highly effective in controlling the disease. This has been driven by the significant toxicity associated with ASCT, albeit of very limited duration and reversible, compared with the newer therapies which can lead to similar degrees of response. Although many clinical trials have confirmed the survival improvements of ASCT vs not receiving this modality, the data have been equivocal with respect to the timing of ASCT following the initial diagnosis.[9-16] In this review, we have examined the data supporting the use ASCT for myeloma, specifically highlighting the pros and cons of an upfront stem cell transplant, and geographical differences in practice patterns and the underlying data that drive these differences.

Is ASCT important in today's treatment paradigm for myeloma?

The relevance of ASCT in the current treatment approaches for myeloma should be examined in the context of the available clinical trial data as well as the alternative treatment approaches in use and the long-term outcomes of MM with the currently available therapies. Several randomized clinical trials, starting from the pivotal trials done by the Intergroupe Francophone Du Myelome (IFM) group in France to the Medical Research Council (MRC) group in the United Kingdom, have demonstrated improved progression-free survival (PFS) and overall survival (OS) with use of ASCT compared with no access to ASCT.[9-16] The results of these phase 3 trials are summarized in Table 1. The phase 3 trials consistently demonstrated improved depth of response as well as higher response rates compared with conventional therapies, translating into improved PFS as well as improved OS, when ASCT was not offered to the patients in the

Table 1. Conventional chemotherapy vs ASCT

Ref.	Year	Treatment arms	Overall response (chemotherapy vs ASCT)	PFS (chemotherapy vs ASCT)	OS (chemotherapy vs ASCT)
Attal et al[9]	1996	Alternating cycles of VMCP/BVAP × 18 cycles vs same regimen × 4-6 cycles followed by ASCT	57% vs 81% ($P < .01$)	5 y: 10% vs 28% ($P = .01$)	5 y: 52% vs 12% ($P = .03$)
Child et al[10]	2003	ABCM × 4-12 cycles vs doxorubicin, cyclophosphamide, and prednisone × 3 cycles followed by ASCT	CR: 8% vs 44% ($P < .01$)	19.6 mo vs 31.6 mo ($P < .01$)	42.3 mo vs 54.1 mo ($P = .04$)
Bladé et al[51]	2005	Alternating cycles of VBMCP/VBAD followed by VBMCP/VBAD × 8 cycles vs ASCT	CR: 11% vs 30% ($P < .01$)	33 mo vs 42 mo (P = NS)	66 mo vs 61 mo (P = NS)
Fermand et al[52]	2005	VMCP until plateau vs VAMP × 3-4 cycles and ASCT	CR: 20% vs 36%	19 mo vs 25 mo ($P = .07$)	47.6 mp vs 47.8 mo ($P = .91$)
Barlogie et al[11]	2006	VAD × 4 cycles and VBMCP vs VAD × 4 cycles and ASCT with/without IFN maintenance		7 y: 16% vs 17% (P = NS)	7 y: 42% vs 37% (P = NS)
Palumbo et al[14]	2014	RD × 4 cycles and MPR × 6 cycles vs RD × 4 cycles and ASCT with/without R maintenance		22.4 mo vs 43 mo ($P < .001$)	4 y: 65.3% vs 81.6% ($P = .02$)
Gay et al[15]	2015	RD × 4 cycles and RCD × 6 cycles vs RD × 4 cycles and ASCT with/without R maintenance		28.6 mo vs 43.3 mo ($P < .0001$)	4 y: 73% vs 86% ($P = .004$)

ABCM, adriamycin; BCNU, cyclophosphamide and melphalan; BVAP, BCNU, vincristine, adriamycin, prednisone; CR, complete response; IFN, interferon; MPR, melphalan, prednisolone, Revlimid; NS, nonsignificant; R, Revlimid; RCD, Revlimid, cyclophosphamide, dexamethasone; RD, Revlimid, dexamethasone; Ref., reference; VAD, vincristine, Adriamycin, dexamethasone; VAMP, vincristine, Adriamycin, melphalan, prednisolone; VBAD, vincristine, BCNU, Adriamycin, dexamethasone; VMCP; vincristine, melphalan, cyclophosphamide, prednisolone; VBMCP, vincristine, BCNU, melphalan, cyclophosphamide, prednisolone.

non-ASCT arm. As treatments for myeloma have evolved, these trials have been criticized as not representing the modern therapies in the control arms, and as a result several trials were designed within the past decade to once again address this question. These trials are also included in Tables 1 and 2 and demonstrate consistent and retained benefit for this treatment modality compared with the more contemporaneous therapies, among patients eligible to undergo ASCT.

Over and above the data from clinical trials, there are compelling arguments for continued use of ASCT as a treatment modality for MM.[17] The most important of these is the unquestionable efficacy of this modality.[18] Used as a 1-time treatment, it provides disease control in nearly all patients with a complete response in nearly one-third and an estimated median PFS of 18 months to 2 years in the absence of any further therapy. The safety of this procedure has improved considerably over the years with treatment-related mortality of <1% in experienced centers, with increasing availability of the modality across institutions large and small.[19,20] The posttransplant course is very predictable with toxicities that are well understood and easily manageable with good supportive care including management of mucositis, infections, and cytopenias requiring transfusion support. There is no denying the acute toxicity of high-dose chemotherapy including the profound cytopenia with the consequent infections and risk of bleeding as well as the mucositis-related symptoms and risk of organ damage. However, there has been all-around improvement in all aspects of ASCT including use of peripheral blood stem cells that can be collected reliably in nearly all patients with judicious use of granulocyte colony-stimulating factor with or without plerixafor, a CXCR4 inhibitor, as well as increasing use of outpatient-based transplant practice, which makes the treatment experience easier.[19,21,22] Given this context, it would not be prudent to discard this therapeutic modality for a disease that remains incurable, at least based on conventional definition of a disease cure.

Early vs delayed ASCT: is the timing relevant?

Even though the utility of ASCT is clear, there has been considerable debate regarding the optimal timing of this approach given the alternate options available today. The very early clinical trials demonstrating the efficacy of ASCT were performed in patients with relapsed myeloma, and subsequently the phase 3 trials demonstrating the survival improvement were conducted in patients with newly diagnosed disease as part of their initial therapy. The alternate approach of delaying ASCT to a later line of therapy at the time of disease recurrence was considered very early on, even as ASCT was being evaluated in the initial clinical trials.[13] Although clinical trials were designed to examine the benefits of early vs delayed ASCT in patients with MM, much of the data asking this question come from retrospective studies that have to be interpreted with caution. A randomized clinical trial specifically examined whether delivering ASCT as part of the initial treatment of myeloma is better than delaying the modality until the time of relapse.[13] The trial not only examined the impact of the 2 approaches on the response and survival end points, but also evaluated the effect on patient-reported outcomes and quality of life. The trial demonstrated that an early transplant was associated with better PFS, but no difference was seen in terms of OS by delaying the ASCT to the time of relapse. This finding highlights the continued efficacy of this modality even in the later lines of therapy. Importantly, the trial demonstrated a significant benefit for early ASCT in terms of time without symptoms and toxicity of therapy (TwiSST), highlighting the durability of disease control with ASCT compared with conventional therapy. These findings have been consistent in subsequent trials that still allowed for patients to receive ASCT at the time of relapse as well as many retrospective studies examining this question, the latter being quite heterogenous in terms of the patients studied, with no clear assessment of why the ASCT was delayed in some (Table 2).[13,23-26] Doubts that have been raised as to whether these findings are still applicable with the current initial treatment approaches have been dispelled by the results of the recent IFM2009 trial that once again demonstrated better PFS, but comparable OS with early or delayed ASCT, respectively.[16] However, the follow-up for this trial remains relatively short and, as with some of the older trials, one might see an OS difference emerge with longer-term follow-up.

If the intent of the upfront therapy in myeloma is to use an approach that will provide the best depth of response and most durable disease control (ie, the best "initial package"), then using an effective induction therapy that includes a proteasome inhibitor and an immunomodulatory drug (IMiD), followed by 1 or 2 transplants and post-ASCT maintenance provides the best outcomes.[16,27] The results of the IFM2009 trial once again confirms this. The trial also demonstrated the effectiveness of high-dose therapy by improving the depth of response as indicted by a nearly 15% improvement in the minimal residual disease–negative (MRD^-) rate with ASCT compared with the modern combination of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRD). Increased depth of response as indicated by MRD negativity has been shown to be a good prognostic factor and an excellent surrogate for PFS improvement. A meta-analysis of multiple clinical trials demonstrated improved PFS as well as improved OS in patients who achieve MRD negativity, and this impact continues to be evident even within the group of patients who have obtained a complete response from their therapy.[28]

One of the perceived benefits of early ASCT had been the limited duration of treatment with the early incorporation of ASCT compared with the non-ASCT approaches that called for prolonged duration of treatment with its attendant toxicity. The current treatment approaches that call for continued maintenance treatment after ASCT potentially take away the advantage of limited duration of therapy with upfront ASCT.[29] Even though patients continue on treatment after ASCT, this is less relevant with current-day treatments that can be given with limited toxicity compared with the traditional chemotherapy approaches. Multiple trials have demonstrated that maintenance treatment with lenalidomide or bortezomib, typically given at a lower dose or less frequently, can be tolerated well for long periods.[30-32]

An argument that has been made in favor of delaying the ASCT to a later time has been the comparable outcome despite nearly one-half of patients in the non-ASCT arms of some trials never receiving an ASCT in a delayed fashion.[11] So, can a delayed approach allow us to spare some patients the toxicity associated with ASCT? We have learned over the years that MM is a very heterogenous disease and it is more than likely that there are patients who may have a very good outcome irrespective of the

Table 2. Early vs delayed ASCT

Ref.	Year	Study type	Induction regimen (early ASCT vs delayed ASCT)	Response (early vs delayed ASCT)	PFS (early vs delayed ASCT)	OS (early vs delayed ASCT)
Fermand et al[13]	1998	P	VAMP × 3-4 cycles and ASCT vs VMCP until plateau and ASCT at relapse	85.7% vs 55.5%	39 mo vs 13 mo	64.6 mo vs 64 mo (P = .92)
Attal et al[16]	2017	P	VRD × 3 cycles and ASCT + VRD × 2 cycles vs VRD × 8 cycles and ASCT at relapse	CR: 59% vs 48% (P = .03)	50 mo vs 36 mo (P < .01)	4 y: 81% vs 82%
Kumar et al[24]	2012	r	TD or RD × 4-6 cycles followed by early or delayed ASCT		20 mo vs 16 mo (P = NS)	4 y: 73% vs 73% (P = .3)
Dunavin et al[23]	2013	r	T-, R-, or V-based induction followed by early or delayed ASCT	≥VGPR: 77% vs 55% (P < .01)	28 mo vs 18 mo (P = .11)	NR vs 83 mo (P = .45)
Remenyi et al[25]	2016	r	57% in early ASCT and 53.2% in delayed ASCT group received novel therapies	CR: 58.1% vs 46.8% (P = .016)	30.2 mo vs 23.3 mo (P = .036)	97.2 mo vs 99.1 mo (P = .77)

CR, complete response; NR, not reached; NS, nonsignificant; P, prospective; r, retrospective; R, Revlimid; RD, Revlimid, dexamethasone; Ref., reference; T, thalidomide; TD, thalidomide, dexamethasone; V, Velcade; VAMP, vincristine, Adriamycin, melphalan, prednisolone; VGPR, very good partial response; VMCP, vincristine, melphalan, cyclophosphamide, prednisolone; VRD, Velcade, Revlimid, dexamethasone.

therapy that they receive.[33] However, in the absence of a reliable marker that would identify these minority of patients upfront, we run the risk of trading the "spared toxicity" for potentially reducing the duration of disease control with the upfront therapy and the impact of the "time without disease relapse" requiring active therapy. It also discounts the possibility that these patients may have done even better with an ASCT at the time of relapse.

A disadvantage though is that a substantial proportion of this minority may have become ineligible for ASCT at the time of relapse for a variety of reasons including advanced age, new comorbidities (which is not uncommon in this older population), or very aggressive disease. This has been highlighted in some of the recent studies delving into reasons for nonutilization of collected stem cells. In fact, it is likely that the OS of the "non-transplanted patients" is not affected as the divergent outcomes of these 2 populations neutralize each other.[34]

ASCT really functions as a platform that can incorporate novel therapies both before and after high dose therapy to improve outcomes. As immune therapies become more mainstream and demonstrate efficacy, ASCT is likely to be a pivotal component in the context of the novel therapies. However, the recent trials once again offer some flexibility for the patients who want to have choices in terms of the timing of the therapies. It is clear that a delay in ASCT to the time of first relapse does not compromise OS; as such, patients may elect to delay ASCT for a variety of reasons. The current level of data does not allow us to identify patients for an early or delayed approach based on clinical characteristics at diagnosis or at the end of induction. The benefit seen with early ASCT is independent of the level of response to induction therapy. Given the benefit seen with deep responses among the high-risk patients, one could argue for use of ASCT early in these patients as that approach gives a better chance at achieving an MRD$^-$ state. The decision regarding timing should be based on a clear discussion of the pros and cons between the patient and the physician.

Geographical differences in ASCT-based approaches: what are the data behind this?

Now, let us take a look at the geographical differences in the application of ASCT for treatment of myeloma and the data that support the different approaches. In general, the typical approach in the European setting is to offer a single or tandem ASCT after 4 to 6 cycles of induction therapy in patients under 65 years of age and selected patients up to 70 years.[35] In the older patients, they often receive treatments that either involve a doublet like Revlimid and dexamethasone or an alkylator-based combination such as bortezomib, melphalan, and prednisone. In contrast, the typical approach in the United States is to initiate induction therapy for myeloma that increasingly uses triplets that contain a proteasome inhibitor, an IMiD, and dexamethasone.[36,37] This is followed by a single ASCT in the upfront setting that is used by ~60% of eligible patients whereas the remaining patients elect to collect the stem cells and use transplant at the time of this relapse.

Transplant eligibility

The phase 3 trials demonstrating the value of ASCT, most of which have been performed by the European myeloma groups, have consistently included patients 65 years of age or younger.[9,12,14-16] The current European guidelines reflect this

approach and use age as a general guideline for transplant eligibility. This is in stark contrast to the practice in the United States, where patients are often transplanted up to 75 years of age and even beyond, albeit with careful patient selection.[38,39] Multiple retrospective studies have demonstrated the efficacy of ASCT is the older patient population and the data support this strategy. This practice pattern has implications on the timing of ASCT as the median PFS with ASCT and maintenance therapy today nearly reaches 4 to 5 years. Hence, a patient who is over 70 years of age, who elects to have a delayed ASCT, has a high probability of not being able to receive the ASCT at the time of relapse. So, an upfront ASCT may be a more prudent approach for a patient who is older, if this approach is being considered.

Induction therapy

The available choices for induction therapy vary considerably in different parts of the world. Although the combination of VRD has become the standard of care in the United States, it is seldom used outside of the clinical trials in Europe and Asia, where other combinations such as bortezomib, and dexamethasone with either thalidomide or cyclophosphamide remain the standard induction regimens.[40] Use of 9 to 12 cycles of VRD followed by lenalidomide maintenance has been studied in phase 3 trials and has been shown to be a well-tolerated approach for patients not going to ASCT; there are more limited data with long-term use of bortezomib, thalidomide, dexamethasone (VTD) or bortezomib, cyclophosphamide, dexamethasone (VCD) in patients not going to ASCT.[16,41] The cumulative toxicity, particularly peripheral neuropathy, limits the long-term use of VTD and may not lend itself to the delayed ASCT approach in transplant-eligible patients. Alternate induction regimens such as lenalidomide and dexamethasone (RD) may be used as initial therapy in patients in whom a delayed transplant is considered.[42] So, the availability of the specific induction regimens may push the practice toward an early or delayed ASCT and can account for some of the geographical differences in the timing of ASCT. Irrespective of the induction regimen used, in patients for whom an early stem cell transplant is being contemplated, this should be done after 4 to 6 cycles of therapy. There is no clear evidence that prolonged induction therapy prior to ASCT alters OS outcomes.[43] The role of changing induction regimen for lack of very good partial response (VGPR) or better was evaluated in an MRC trial, where additional therapy with a different regimen prior to ASCT led to deeper responses, and improved PFS, but no improvement in OS. Currently, most of the clinical trials and standard practice use a fixed duration of induction (4-6 cycles) and then proceed to ASCT irrespective of the depth of response.

Role of tandem ASCT

The role of tandem ASCT remains an area of contentious debate in MM.[44-47] After the initial phase 3 trials demonstrating a survival advantage for this approach, its use declined considerably, especially in the US practice as the subsequent trials failed to demonstrate an OS advantage for the tandem approach. More recently, there has been a surge in interest in this approach for selected patients based on a combination of additional analysis of previous trials as well as new phase 3 trials.[46] Although the OS benefit has been modest across the entire transplant-eligible patient population, there appears to be a selective advantage for patients with high-risk cytogenetic abnormalities as has been observed in the European studies. A collective evaluation of several European studies suggested better outcome for patients with high-risk cytogenetics with the tandem approach. The EMN02 trial demonstrated an OS advantage for tandem ASCT, especially evident in the patients with high-risk cytogenetics. However, the STAMINA trial conducted in the United States failed to show any OS or PFS benefit for tandem ASCT and the data for the high-risk patients have not become available at this time. Differences in the 2 trials may be related to nearly one-third of the patients in the STAMINA trial not receiving a tandem transplant as intended or due to the prolonged induction allowed, or the lack of use of novel-agent triplets in the European trial. Tandem ASCT continues to be used extensively in the European setting especially in clinical trials and by the German myeloma groups. If tandem ASCT is considered for the specific populations where it has the maximum impact, that again would lead one down the path of an early ASCT.

Consolidation

The role of posttransplant consolidation outside of the tandem ASCT has also been the subject of many clinical trials. The most recent trials specifically asking this question had been the EMN02 trial in the Europe and the STAMINA trial in the United States. Although this aspect of the transplant does not specifically drive the choice between early or delayed ASCT, it is certainly an area of divergence in the practice across the Atlantic. The European data suggest a distinct benefit for 2 cycles of posttransplant consolidation with VRD in patients receiving initial induction therapy with VCD and is reflected in the current practice across several of the European groups. However, the US data did not show a benefit for the VRD consolidation, likely explained by the preponderance of patients receiving VRD as induction therapy and a significant proportion of patients receiving >4 cycles of induction with VRD and thus reducing the likelihood of additional benefit with repetition of the same regimen post-ASCT. So, it is likely that the benefit is linked to the cumulative amount of combination therapy given, whether as induction pretransplant or consolidation posttransplant.

Maintenance

Posttransplant maintenance has become the standard of care for patients undergoing ASCT for myeloma. Several phase 3 trials as well as a metanalysis of these trials have demonstrated an OS advantage to the tune of 2.5 years for patients receiving lenalidomide maintenance post–upfront ASCT.[29-31] Although there is consensus in terms of the utility of maintenance therapy, there appears to be a distinct *trans*-Atlantic difference in terms of the ideal duration of lenalidomide maintenance. Many of the European trials have capped the maintenance duration at 1 or 2 years and reflect the current practice there, but the US trial used maintenance until relapse. The current practice in the United States appears to be split across continuous maintenance until progression or 2 years of maintenance. Ongoing clinical trials are examining the question of ideal duration of maintenance, but it is reasonable to consider at least 2 years of maintenance based on the current data. Importantly, MRD-directed approaches for determining the ideal duration of maintenance are being evaluated in prospective randomized trials. Another consideration that has been driving the limited duration of maintenance has been the increased risk of second malignancies seen among patients receiving lenalidomide maintenance, a risk that appears to be cumulative over time. In addition, certain groups of patients such as those with high-risk MM and those with International Staging System (ISS) stage III do not appear to benefit from lenalidomide maintenance and are often considered for bortezomib-based maintenance.

Quality-of-life aspects

The differences in the approach across the Atlantic are also driven to some extent by the data from phase 3 clinical trials that have systematically examined measures of quality of life, especially the impact of therapy. Although there are limited data that compare early vs delayed ASCT in the era of novel drugs, the initial trial by Fermand et al clearly demonstrated an improvement in the time without symptoms and toxicity related to therapy among those who received an upfront ASCT.[13] Ongoing studies continue to examine patient-reported outcomes in the context of ASCT in comparison with the known transplant treatment approaches currently available with the newer therapies. One could argue that, in the context of maintenance therapy after stem cell transplant, the impact of time without therapy may not be that profound, as was found in the earlier phase 3 clinical trials. But, considering that many of the novel treatments are well tolerated, the impact of maintenance therapy used today may not be the same as was seen with continuous conventional chemotherapy approaches.

Financial aspects

Reimbursement patterns in the different health care systems also continue to be a major driver of treatment approaches. In the United States, stem cell transplantation is covered both by private insurance as well as Medicare, allowing a larger spectrum of patients to potentially undergo the procedure in contrast to the situation elsewhere, where stem cell transplantation is often limited to patients under 65 years of age. The ability to use a triple combination such as VRD prior to stem cell transplantation and potentially continuing on the therapy in case of delayed stem cell transplantation also contributes to many patients deciding to delay the stem cell transplant in the setting of excellent response with these effective initial therapies, which also are relatively well tolerated. In contrast, this induction regimen is not covered by the health care systems in many parts of Europe, leading to the use of other combinations such as VCD and VTD, both of which can be given for a limited number of cycles followed by stem cell transplantation. This will likely change in the near future as the VRD becomes widely reimbursed. Although stem cell transplantation has been considered as an expensive therapy, the price tag for these multidrug combinations, especially when given over a long period of time, can easily exceed the cost of stem cell transplantation by several fold.[48] Within the limitations of the cost, adding stem cell transplantation to the available drugs used in induction and maintenance allows these patients to get the best possible response with their initial line of therapy and likely explains the increased use of this procedure in the European setting. In fact, some recent studies have suggested that an upfront transplant may be a more cost-effective strategy for treatment of myeloma.[49]

Salvage ASCT

The concept of repeating ASCT at the time of myeloma relapse has been around right from the beginning, and, in fact, was the setting in which SCT was initially studied. It is increasingly a common practice to collect enough stem cells for more than 1 transplant with the intent to use the remaining cells for future transplants. A prospective trial from the United Kingdom, albeit using a conventional[50] chemotherapy-based regimen as control, demonstrated superior PFS for salvage ASCT. Studies suggest this approach to be particularly beneficial for patients with prolonged response to the initial transplant, with or without maintenance. In general, a duration of response of 18 months or more with first transplant in the unmaintained setting or over 36 months in the maintained setting is considered adequate for consideration of salvage ASCT. Another argument that has been proposed in favor of a second salvage ASCT has been the ability of this procedure to reset the bone marrow function, which may be diminished by the cumulative hematological toxicity related to many of the drugs that we currently use for treatment of this disease. In such a setting, the stem cell transplant not only allows for excellent control of the underlying tumor, but also improves the cellularity and function of the bone marrow thus allowing for continued application of the different therapies for control of the disease.

Conclusion

After nearly 3 decades of debate and several randomized phase 3 trials, it is clear that ASCT as a treatment modality has stood the test of time. It continues to be an effective modality to provide durable disease control for myeloma even with the introduction of novel agents. Given the depth of response and the PFS advantage seen in phase 3 trials, ASCT should be considered as part of the initial therapy. However, without a clear OS advantage to early ASCT based on the data available today, a delayed ASCT is a reasonable approach should the patient and the treating physician desire to pursue that approach after a thorough discussion of the pros and cons of either approach, as discussed in this article.

Authorship

Contribution: S.K.K. wrote the manuscript; and F.K.B. and S.V.R. reviewed and edited the manuscript.

Conflict-of-interest disclosure: S.K.K. received consulting fees, paid to the institution, from Celgene, Takeda, Janssen, KITE, Merck, Abbvie, Medimmune, Genentech, Oncopeptides, and Amgen. The remaining authors declare no competing financial interests.

Correspondence: Shaji K. Kumar, Division of Hematology, Mayo Clinic, Rochester, MN 55905; e-mail: kumar.shaji@mayo.edu.

Footnote

Submitted 22 August 2018; accepted 15 December 2018. Prepublished online as *Blood* First Edition paper, 26 December 2018; DOI 10.1182/blood-2018-08-825349.

REFERENCES

1. Kumar SK, Rajkumar V, Kyle RA, et al. Multiple myeloma. *Nat Rev Dis Primers*. 2017;3:17046.
2. Kumar SK, Rajkumar SV. The multiple myelomas - current concepts in cytogenetic classification and therapy. *Nat Rev Clin Oncol*. 2018;15(7):409-421.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003; 78(1):21-33.
4. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014; 28(5):1122-1128.
5. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood Adv*. 2017;1(4):282-287.

6. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc*. 2016;91(1):101-119.

7. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008; 111(5):2516-2520.

8. Barlogie B, Alexanian R, Dicke KA, et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. *Blood*. 1987;70(3): 869-872.

9. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med*. 1996; 335(2):91-97.

10. Child JA, Morgan GJ, Davies FE, et al; Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348(19):1875-1883.

11. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321 [published correction appears in *J Clin Oncol*. 2006;24(17):2687]. *J Clin Oncol*. 2006;24(6):929-936.

12. Bladé J, Esteve J, Rives S, et al. High-dose therapy autotransplantation/intensification vs continued standard chemotherapy in multiple myeloma in first remission. Results of a non-randomized study from a single institution. *Bone Marrow Transplant*. 2000;26(8):845-849.

13. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood*. 1998;92(9): 3131-3136.

14. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014; 371(10):895-905.

15. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(16):1617-1629.

16. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14): 1311-1320.

17. Dhakal B, Szabo A, Chhabra S, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(3): 343-350.

18. Chute JP. Autologous stem cell transplantation for multiple myeloma: underutilized but highly effective [published online ahead of print 11 June 2018]. *J Natl Cancer Inst*. doi:10.1093/jnci/djy102.

19. Gertz MA, Buadi FK, Hayman SR, et al. Safety outcomes for autologous stem cell transplant in multiple myeloma. *Mayo Clin Proc*. 2018; 93(1):56-58.

20. Sanchez L, Sylvester M, Parrondo R, Mariotti V, Eloy JA, Chang VT. In-hospital mortality and post-transplantation complications in elderly multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation: a population-based study. *Biol Blood Marrow Transplant*. 2017;23(7): 1203-1207.

21. Martino M, Ciavarella S, De Summa S, et al. A comparative assessment of quality of life in patients with multiple myeloma undergoing autologous stem cell transplantation through an outpatient and inpatient model. *Biol Blood Marrow Transplant*. 2018;24(3):608-613.

22. Micallef IN, Stiff PJ, Stadtmauer EA, et al. Safety and efficacy of upfront plerixafor + G-CSF versus placebo + G-CSF for mobilization of CD34(+) hematopoietic progenitor cells in patients ≥60 and <60 years of age with non-Hodgkin's lymphoma or multiple myeloma. *Am J Hematol*. 2013;88(12): 1017-1023.

23. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma*. 2013;54(8): 1658-1664.

24. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer*. 2012; 118(6):1585-1592.

25. Remenyi P, Varga G, Mikala G, et al. Early versus delayed autologous stem cell transplantation and interferon maintenance in multiple myeloma: single-center experience of 18 years. *Transplant Proc*. 2016;48(1): 177-184.

26. Richardson PG, Laubach JP, Munshi NC, Anderson KC. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? *Hematology Am Soc Hematol Educ Program*. 2014;2014: 255-261.

27. Cavo M, Tacchetti P, Patriarca F, et al; GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376(9758): 2075-2085.

28. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;3(1):28-35.

29. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;35(29):3279-3289.

30. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; 366(19):1770-1781.

31. Attal M, Lauwers-Cances V, Marit G, et al; IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19): 1782-1791.

32. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol*. 2012;30(24):2946-2955.

33. Ravi P, Kumar SK, Cerhan JR, et al. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. *Blood Cancer J*. 2018;8(3):26.

34. Kansagra A, Gonsalves WI, Gertz MA, et al. Analysis of clinical factors and outcomes associated with nonuse of collected peripheral blood stem cells for autologous stem cell transplants in transplant-eligible patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2018;24(10):2127-2132.

35. Gay F, Engelhardt M, Terpos E, et al. From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. *Haematologica*. 2018;103(2):197-211.

36. Kumar SK, Callander NS, Alsina M, et al. Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(2):230-269.

37. Gonsalves WI, Buadi FK, Ailawadhi S, et al. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus statement [published online ahead of print 9 July 2018]. *Bone Marrow Transplant*. doi: 10.1038/s41409-018-0264-8.

38. Winn AN, Shah GL, Cohen JT, Lin PJ, Parsons SK. The real world effectiveness of hematopoietic transplant among elderly individuals with multiple myeloma. *J Natl Cancer Inst*. 2015;107(8).

39. Auner HW, Garderet L, Kröger N. Autologous haematopoietic cell transplantation in elderly patients with multiple myeloma. *Br J Haematol*. 2015;171(4):453-462.

40. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068): 519-527.

41. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127(21): 2569-2574.

42. Benboubker L, Dimopoulos MA, Dispenzieri A, et al; FIRST Trial Team. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014; 371(10):906-917.

43. Vij R, Kumar S, Zhang MJ, et al. Impact of pretransplant therapy and depth of disease response before autologous transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21(2):335-341.

44. Moreau P, Hullin C, Garban F, et al; Intergroupe Francophone du Myélome group. Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomized IFM 99-04 protocol. *Blood*. 2006;107(1):397-403.

45. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. *Br J Haematol*. 2016;173(5):731-741.

46. Cavo M, Gay FM, Patriarca F, et al. Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: an analysis of phase 3 EMN02/HO95 study [abstract]. *Blood*. 2017;130(suppl 1). Abstract 401.

47. Attal M, Harousseau JL, Facon T, et al; InterGroupe Francophone du Myélome. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349(26):2495-2502.

48. Huntington SF, Weiss BM, Vogl DT, et al. Financial toxicity in insured patients with multiple myeloma: a cross-sectional pilot study. *Lancet Haematol*. 2015;2(10):e408-e416.

49. Pandya C, Hashmi S, Khera N, et al. Cost-effectiveness analysis of early vs. late autologous stem cell transplantation in multiple myeloma. *Clin Transplant*. 2014;28(10):1084-1091.

50. Cook G, Williams C, Brown JM, et al; National Cancer Research Institute Haemato-oncology Clinical Studies Group. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [intensive trial]): a randomised, open-label, phase 3 trial [published correction appears in *Lancet Oncol*. 2014;15(9):e365]. *Lancet Oncol*. 2014;15(8):874-885.

51. Bladé J, Rosiñol L, Sureda A, et al; Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA). High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106(12):3755-3759.

52. Fermand JP, Katsahian S, Divine M, et al; Group Myelome-Autogreffe. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol*. 2005;23(36):9227-9233.