Stem-cell transplantation in multiple myeloma: how far have we come?

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Abstract: High-dose therapy (HDT) and autologous stem-cell transplantation (ASCT) has historically been an essential part of multiple myeloma (MM) management since early studies demonstrated its efficacy in relapsed disease, and subsequent phase III trials demonstrated better responses and improved survival with this modality compared with standard chemotherapy. With further advances in the MM treatment landscape, including the development of potent novel agents, there has been an increasing debate around various aspects of ASCT, including the optimal timing, role of single *versus* tandem ASCT, and the practice of consolidation and maintenance therapy post-ASCT. Routine incorporation of the novel agents at each of the treatment phases, induction, consolidation when used, and maintenance has led to better responses as reflected by increasing rates of minimal residual disease (MRD) negativity, longer progression-free survival (PFS) with improvement in overall survival (OS) and in some of the trials. The phase III trials over the last decade have provided significant clarity on the current approach, and have raised important questions regarding the applicability of this modality in all patients. This review aims to summarize the latest literature in the field and discusses how these findings impact the practice of ASCT today.

Keywords: multiple myeloma, stem-cell transplantation, autologous

Introduction

High-dose therapy (HDT) followed by autologous stem-cell transplantation (ASCT) has been the standard of care for eligible multiple myeloma (MM) patients for over two decades.[1] A study by the Intergroupe Francais Du Myelome (IFM) group published in 1996 showed that ASCT improved 5-year overall survival rates (OS) compared with conventional chemotherapy alone (52% *versus* 12%, $p = 0.03$), at a time when the median OS for MM using conventional chemotherapy was approximately 3 years.[2] In the early 2000s, a multicenter study by the Medical Research Council (MRC) of the United Kingdom showed that ASCT increased median survival by approximately 1 year (54.1 months *versus* 42.3 months) when compared with traditional chemotherapy.[3] The induction chemotherapy used in both studies were mainly alkylating agents, anthracyclines, and corticosteroids.[2,3]

MM treatment has advanced significantly over the last two decades following these landmark studies and the survival rate has significantly improved following the development of novel agents.[4,5] Combinations of proteasome inhibitor (PI) and immunomodulatory agents (IMiD) as induction therapy have been proved to be well tolerated and effective[6–10] and have been widely used in the United States and Europe. Over the last 5 years, many potent novel agents have been approved and have improved our ability to achieve improved responses.[10–12]

This review will discuss the role of ASCT in the current MM treatment landscape, the current practice of ASCT, including the use of consolidation and maintenance therapy post-ASCT, and the role of tandem ASCT and allogeneic stem-cell transplantation in MM.

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Table 1. Phase III trials comparing regimens with and without ASCT.

Author	Study design	Patient population (with *versus* without ASCT)	Treatment regimen (with *versus* without ASCT)	PFS (with *versus* without ASCT)	OS (with *versus* without ASCT)
Gay et al.[13]	Randomized, phase III trial	256 patients (127 *versus* 129), ≤65 years old	RD × 4 and (ASCT *versus* RCD × 6) + R maintenance	Median PFS: 43.3 months *versus* 28.6 month (p < 0.0001)	4-year OS: 86% *versus* 73% (p = 0.004)
Palumbo et al.[14]	Randomized, phase III trial	273 patients (141 *versus* 132), ≤65 years old	RD × 4 and (ASCT *versus* MPR × 6) ± R maintenance	Median PFS 43.0 months *versus* 22.4 months; (p < 0.001)	4-year OS: 81.6% *versus* 65.3% (p = 0.02)
Cavo et al.[15]	Randomized, phase III trial	1192 patients (695 *versus* 497), ≤65 years old	Bortezomib-based induction x 3-4 + (ASCT vs VMP x 4) + (VRD vs no consolidation) + R maintenance	3-year PFS: 64% vs 57% (P=0.002)	3-year OS: 85% in both treatment arms
Attal et al.[16]	Randomized, phase III trial	700 patients (350 *versus* 350), ≤65 years old	VRD × 3 + (ASCT *versus* VRD × 5) + VRD × 2 + R maintenance	Median PFS (50 months *versus* 36 months; p < 0.001)	4-year OS: 81% *versus* 82% (p = 0.87)

ASCT, Autologous Stem-cell Transplant; EFS, event-free survival; MPR, melphalan–prednisone–lenalidomide; OS, overall survival; PAD, bortezomib, doxorubicin, and dexamethasone; PFS, progression-free survival; R, lenalidomide; RD, lenalidomide–dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; VMP, bortezomib-melphalan-prednisone; VRD, bortezamib–lenalidomide–dexamethasone.

The role of upfront ASCT in MM treatment landscape in the current era of novel agents

ASCT remains an important part of MM treatment in the current era of novel agents

In line with the continued improvement of outcomes with novel agents, the value of ASCT in the MM treatment model has been a topic of debate. A number of phase III studies have been performed over the last decade to address whether ASCT retains its relevance in the era of modern therapies (Table 1). A randomized, multicenter, phase III trial carried out by Gay and colleagues randomized patients to receive either chemotherapy plus lenalidomide *versus* ASCT after induction therapy with lenalidomide and dexamethasone showed significantly improved progression-free survival (PFS) with ASCT when compared with chemotherapy and lenalidomide (median PFS 43.3 months *versus* 28.6 months, p < 0.0001).[13] Palumbo and colleagues demonstrated in an open-label, randomized, phase III study, that compared ASCT with melphalan–prednisone–lenalidomide (MPR) following induction therapy with lenalidomide and dexamethasone, that both PFS and OS were significantly longer with ASCT than with MPR (median PFS 43.0 months *versus* 22.4 months, p < 0.001, and 4-year OS, 81.6% *versus* 65.3%; p = 0.02).[14] However, it is important to note that these studies did not include a PI as

induction therapy triplet or consolidation that is the current standard of care. The EMN02/HO95 randomized, phase III study showed that when compared with bortezomib–melphalan–prednisone (VMP) dose-intensification, ASCT following bortezomib-based induction treatment was associated with improved PFS.[15]

A large randomized, open-label, phase III trial carried out by the IFM group randomized patients to receive induction therapy with three cycles of bortezomib, lenalidomide, and dexamethasone (VRD) and then consolidation therapy with either five additional cycles of VRD or ASCT followed by two additional cycles of VRD.[16] Both groups received maintenance therapy with lenalidomide for 1 year.[16] The ASCT group had significantly improved median PFS (50 months *versus* 36 months; p < 0.001), the percentage of patients with a complete response (CR) (59% *versus* 48%, p = 0.03), and the percentage of patients who achieved minimal residual disease (MRD) negativity (79% *versus* 65%, p < 0.001), when compared with the VRD group.[16] There was, however, no difference in OS at 4 years.[16] The findings of these phase III trials, demonstrate consistent benefit in terms of higher response rates, degree of response, and improved PFS for ASCT compared with the more contemporary therapies, has led to the current recommendation that continues

to support the incorporation of ASCT into the MM treatment process.[13]

Early *versus* delayed ASCT in the current era of novel agents

The study results previously described show improved PFS and improved response with upfront ASCT and this remains a standard of care treatment for transplant-eligible newly diagnosed MM patients. The OS benefit, however, remains unclear. Therefore, there has been a considerable debate about the optimal timing of ASCT and the use of early *versus* delayed ASCT in newly diagnosed MM patients.

Before the introduction of novel agents Fermand and colleagues showed improved PFS and shorter duration of chemotherapy in early *versus* late ASCT in newly diagnosed MM patients, but no difference in OS.[26] Despite the lack of OS benefit, however, findings by Fermand and colleagues demonstrated that early ASCT was associated with significant time without symptoms and toxicity of therapy (TwISST), therefore, making a compelling case for the continued use of ASCT early in the treatment regime.[26] In addition, a meta-analysis by Koreth and colleagues of the early trials of ASCT in MM showed PFS benefit without OS benefit with early ASCT in newly diagnosed MM patients.[27]

In the era of novel agents, studies have shown that early ASCT was not associated with significant OS benefit. Kumar and colleagues demonstrated that in transplant-eligible MM patients receiving IMiD as initial therapy followed by early stem-cell mobilization, delayed ASCT resulted in similar OS when compared with early ASCT.[28] Dunavin and colleagues demonstrated that both early and delayed ASCT were viable options for MM patients receiving induction treatment with novel targeted therapies with no significant difference in OS.[29] The IFM 2009 study, as previously described, showed improved PFS but not OS.[16] A recently published systematic review and meta-analysis confirmed that early ASCT has been associated with prolonged PFS, but not OS.[30]

These studies suggest that while early ASCT is likely to be associated with the best level of response and the most comprehensive disease control, delayed ASCT does not compromise OS and remains an option today with the introduction of novel agents if, for some personal or logistical reasons, upfront ASCT is not desired or is not feasible. It is, however, important to note that because early ASCT is associated with longer PFS, it might be associated with longer treatment-free intervals, that might be important for patient's quality of life. Clear discussions between physicians and their patients about the advantages and disadvantages of such an approach are important.

Tandem ASCT

Before the introduction of novel agents, tandem ASCT was used as part of a 'total therapy' regimen by the University of Arkansas group using multiregimen induction and tandem ASCT followed by interferon maintenance that showed a progressive increase in CR rates with continuing therapy.[31] A randomized trial carried out by the IFM group before novel agent induction therapy was available showed that when compared with a single ASCT, tandem ASCT improved OS among patients with MM, although this was restricted to patients who had not achieved a very good partial response (VGPR) after the first ASCT.[32] Several other trials, performed before the introduction of novel agents, have shown event-free survival (EFS) but not OS benefit for tandem ASCT.[32–34] This has led to a decline in the use of tandem ASCT, especially in the United States.

With the introduction of novel agents, there has been increased interest in the use of tandem ASCT for selected patients. An integrated analysis of patient-level data from European studies showed the possible beneficial role of tandem ASCT in improving outcomes for newly diagnosed MM patients with poor prognosis, in particular, for those who failed to achieve CR with bortezomib as part of induction therapy and who had a high-risk cytogenetics profile such as t(4;14), deletion of 17p, or both, who had not achieved CR after induction therapy (5-year OS 70% *versus* 17%).[35] A consensus by the International Myeloma Working Group in 2016 recommended HDT plus double ASCT for patients with high-risk cytogenetics.[36]

In recent years, there have been a number of phase III studies investigating this issue. The EMN02/HO95 study demonstrated that tandem ASCT was superior to single ASCT in terms of prolonged OS for the poor prognosis subgroups of patients with advanced Revised International Staging System (R-ISS) disease stage and

high-risk cytogenetic profile.[15] An important caveat was that the induction therapy used in this trial was bortezomib–cyclophosphamide–dexamethasone rather than the PI-IMiD combination routinely used in the United States.[15]

In contrast, the recently published results of the prospective, randomized, phase III BMT–CTN 0702 trial showed that second ASCT or additional consolidation with VRD following the first upfront ASCT did not improve PFS or OS in both standard and high-risk patients.[37] The trial results recommended that single ASCT and lenalidomide maintenance should remain as the standard approach.[37] Approximately half of the patients in this trial received VRD as induction therapy and were then distributed evenly in each arm. One of the arguments for the difference in result with the EMN02/HO95 trial has been the use of the more potent novel agent triplets used in the BMT–CTN study, often given for up to 12 cycles prior to transplant, might suggest that more potent or prolonged induction therapy could negate the benefit of intensive post-ASCT interventions including tandem ASCT or VRD consolidation. In addition, the BMT–CTN 0702 study, unlike the EMN02/H095 study, included patients with high β_2 microglobulin in the high-risk arm, making it difficult to discern whether tandem ASCT would have a selected benefit in the specific subset of patients with high-risk cytogenetics.[37]

A 10-year follow-up of three randomized phase III studies following induction therapy with bortezomib-thalidomide-dexamethasone (VTD) or bortezomib–doxorubicin–dexamethasone (PAD) showed that tandem ASCT resulted in improved PFS [median: 47 *versus* 38 months; hazard ratio (HR) 0.76, *p* = 0.0008] and OS (estimated 10-year probability: 58% *versus* 47%; HR 0.69, *p* = 0.0002) when compared with single ASCT.[38]

In view of these conflicting results, the role of tandem ASCT in MM remains unclear although it may be considered in patients with high-risk cytogenetics, in particular, those who did not receive a novel triplet combination or those with a lower than VGPR response following their first ASCT.

Current practice of ASCT in MM
There have been many advances in the field of ASCT that have affected the current practice of ASCT in MM. In this section, we will further describe the eligibility for ASCT, optimal induction therapy prior to ASCT, mobilization, stem-cell collection, conditioning regimen for ASCT, and consolidation and maintenance therapy post-ASCT.

Eligibility for ASCT
Although most trials evaluating ASCT in MM historically used an age cut-off of ≤65 years old to select eligible patients, the number of patients undergoing ASCT in older age groups has significantly increased over the past years.[39] Many studies have shown that age alone does not have any effect on the outcomes following ASCT in patients with MM.[40–42] An analysis of 946 MM patients aged ≥70 years at ASCT by the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that older subjects selected for ASCT obtained similar antimyeloma benefits without higher nonrelapse mortality, relapse rate, or PFS.[42] A study of 207 MM patients aged 70–76 years old at ASCT treated at the Mayo Clinic showed that ASCT was well tolerated and had noninferior PFS and OS when compared with younger patients.[41]

Careful patient selection remains crucial and assessment of frailty and significant comorbidities play important roles in determining transplant eligibility. ASCT, in general, is avoided for patients with poor performance status or significant cardiac failure.[43] Renal impairment is, however, not an absolute contraindication to ASCT. In a large database study, ASCT was observed to be well tolerated in patients with moderate and severe renal impairment at the time of ASCT.[44] A retrospective registry evaluation suggested that a higher score of hematopoietic stem-cell transplant co-morbidity index (HCT-CI) score typically used for allogeneic stem-cell transplantation (allo-SCT), was associated with inferior OS in ASCT for MM[45] and might be used to help with ASCT eligibility assessment.

Induction therapy prior to ASCT
For the transplant-eligible MM patients, previous studies have shown that melphalan can impair the yield of stem-cell collection and should be avoided as part of induction therapy.[46,47] Following the introduction of novel agents, a triplet regimen is the current standard of care based on the trials demonstrating that a triplet was better than a

doublet regimen.[9,48,49] The VRD combination was shown to be effective compared with the lenalidomide/dexamethasone (Rd) doublet both in terms of PFS and OS in a large phase III trial[9,16,48] and is currently the regimen of choice for induction therapy for transplant-eligible MM patients in the United States. In addition, the combination of PI and IMiD has proved to be superior to the combination of PI and cyclophosphamide in terms of the level of response, although it may come at a higher rate of toxicity in the context of thalidomide.[8,10,48]

With the increasing approval of more novel agents that could soon be used upfront, carfilzomib and daratumumab are potentially an important part of induction therapy prior to ASCT. The FORTE trial showed that the carfilzomib, lenalidomide, and dexamethasone combination is a potential induction therapy prior to ASCT to achieve an increased response and in 95% of cases, stem-cells could be collected successfully following treatment.[10] The Cassiopeia trial explored the addition of daratumumab to VTD therapy and demonstrated increased responses, higher MRD negativity, and improved PFS of the quadruplet therapy compared with the triplet therapy.[50] The phase II Griffin trial showed promising result with a (Daratumumab-VRD Dara–VRD) combination as the induction therapy prior to ASCT and that the inclusion of daratumumab as part of induction therapy did not negatively impact stem-cells mobilization.[51]

With the widespread use of lenalidomide, it is important to note that the increased duration of lenalidomide therapy has been shown to be associated with a decreased stem-cell collection yield[52,53] Therefore, it is recommended that a peripheral blood stem-cell (PBSC) collection is carried out within 6 months of initiation of lenalidomide therapy to reduce stem-cell collection failure, particularly in older patients.[52]

The achievement of a high-quality response following induction therapy has been shown to be associated with extended PFS after ASCT.[6,54] However, the level of response with induction therapy prior to ASCT does not appear to affect survival outcome and is not a key determinant whether patients should proceed with ASCT. A study of ASCT recipients carried out between 1995 and 2010 reported to the CIBMTR evaluating the level of response prior to ASCT showed that although additional therapy pre-ASCT for patients who achieved less than a (partial response PR) would deepen the response, it was not associated with survival benefit.[55] In addition, a study of 596 patients who underwent ASCT at the Mayo Clinic between 2007 and 2014 showed that prolonging the duration of induction therapy beyond 4 months prior to ASCT did not impact survival.[56] Because of these findings, it is common practice that there is a fixed duration of between 4 to 6 months for induction therapy before proceeding to ASCT regardless of the level of response. A prospective trial evaluating the role of additional therapy with a different combination in patients failing to achieve a VGPR or better with induction therapy performed by the MRC demonstrated an improved PFS with the additional therapy without any impact on the post-ASCT OS.

Mobilization and stem-cell collection for ASCT

For ASCT, a minimum dose of 2×10^6 CD34+ cells/kg for a single transplant should be targeted and $>3–4 \times 10^6$ CD34+ cells/kg is optimal for successful engraftment.[57,58] Because the stem-cell yield is predicted to decrease along with more exposure to chemotherapy,[46,47] or lenalidomide,[52] it is recommended to collect enough stem-cells for two or more ASCTs in case another ASCT is needed for tandem or salvage ASCT.[59]

The current practice of stem-cell collection involves collecting PBSC *via* apheresis after mobilization of hematopoietic stem-cells from bone marrow to the peripheral blood. Mobilization with granulocyte colony-stimulating factor (G-CSF) is commonly used and recent studies have shown that the addition of plerixafor, a *CXCR4* antagonist, could improve stem-cell yield further.[60,61] A common practice is to mobilize with G-CSF and if it is predicted that the stem-cell yield is not enough based on the peripheral blood CD34+ measurement, or initial stem-cell apheresis count, plerixafor will be added.

Although the combination of G-CSF and plerixafor have been shown to be effective, plerixafor is expensive and might not be readily available. Other options for mobilization include chemomobilization.[62] For chemomobilization, to the best of our knowledge, there is no standard mobilization regimen, although high-dose cyclophosphamide is commonly used.[63] Combinations

of vinorelbine and cyclophosphamide (Vino-Cy) have proved to be effective with shorter times to achieve adequate stem-cell yield and less toxicity when compared with high-dose cyclophosphamide, however, with a slightly lower stem-cell collection yield.[64] Other regimens including cytarabine plus G-CSF have been shown to result in better stem-cell yield than G-CSF alone[65] or cyclophosphamide plus G-CSF.[66] Patients can also be collected successfully on the rebound from intense chemotherapy when regimens like VDT PACE are employed for treatment of the disease. Despite the high cost of plerixafor, it is potentially cost-effective because of increased yield and reduced toxicities, therefore, reducing the need for additional G-CSF use and hospitalization.[67]

Conditioning regimen for ASCT

HDT with melphalan 200 mg/m^2 remains the standard conditioning regimen and studies have shown that this dose is associated with the optimal balance between efficacy and toxicity. A prospective, multicenter phase III study by Palumbo and colleagues showed that melphalan 200 mg/m^2 was associated with longer median PFS and median time to progression (TTP) when compared with melphalan 100 mg/m^2, although no difference in OS was noted.[68] The EBMT Chronic Malignancies Working Party in the Collaboration To Collect Autologous Transplant Outcomes In Lymphoma And Myeloma (CALM) study reported that there was improved PFS, OS, and relapse rate with melphalan 200 mg/m^2 in patients transplanted in less than partial response when compared with melphalan 140 mg/m^2.[69] The IFM 9502 randomized trial showed that melphalan 200 mg/m^2 is less toxic and as effective as 8 Gy total body irradiation with melphalan 140 mg/m^2 as a conditioning regimen.[70] In contrast, higher doses of melphalan at 280 mg/m^2 have not been shown to improve survival.[71,72]

A few other combinations of conditioning regimen have been evaluated. A phase II trial with a matched-pair comparison of high-dose gemcitabine, busulfan, and melphalan when compared with melphalan alone showed that this combination was associated with improved PFS and OS but at the expense of greater toxicities.[73] A phase III study of the IFM group (IFM 2014-02) evaluating bortezomib and high-dose melphalan *versus* high-dose melphalan alone showed no difference in CR rate, PFS, and OS.[74] Another study showed that a busulfan–melphalan combination was effective and tolerated with an overall response (OR) rate after ASCT of 94.0%, including 43.5% with a stringent CR, 27.3% with VGPR, and 23.2% with partial response.[75] In addition, when compared with melphalan alone, it has been shown to improve PFS but no difference in OS, however, median follow-up remains too short at 28.1 months.[76]

Melphalan dose was recommended to be adjusted to 140 mg/m^2 for significant renally impaired or dialysis-dependent patients.[77] In elderly patients, although melphalan 200 mg/m^2 has been shown to be well tolerated and effective,[78] careful patient selection is crucial. A dose reduction of melphalan to 140 mg/m^2 should be based on careful assessment of frailty and comorbidities rather than on age alone.[41] The lower dose of melphalan in older patients and in those with renal insufficiency does not appear to compromise the efficacy of the approach.

Consolidation therapy Post-ASCT

Several studies have shown that consolidation therapy after ASCT improved the level of response and PFS, however, no OS benefit has been shown.[79–81] The evaluation of consolidation followed by maintenance therapy *versus* maintenance therapy alone in newly diagnosed, transplant-eligible MM patients in the randomized phase III EMN02/HO95 trial showed improved PFS with VRD consolidation across most predefined subgroups, but not in patients with high-risk cytogenetics.[82] As previously described, the recently published result of a prospective, randomized, phase III BMT–CTN 0702 trial showed that consolidation with VRD as post-ASCT intervention did not improve PFS or OS in both standard and high-risk patients. The number of patients with CR and sCR (stringent CR) at enrolment were similar in each arm. Currently, routine use of consolidation therapy post-ASCT cannot be recommended. It remains an option for patients who have not had optimal response post-ASCT.

Maintenance therapy post-ASCT

Maintenance therapy post-ASCT has now been recognized as an integral part of MM therapy in

view of the incurable nature of MM and its ability to prolong the duration of remission. Importantly, a pooled analysis of the GIMEMA-MM-03-05 and RV-MM-PI-209 trials showed that even in patients with CR, maintenance therapy significantly improved PFS and OS.[83] A meta-analysis carried out by Munshi and colleagues. showed that thalidomide and lenalidomide maintenance therapies were able to improve the rate of MRD negativity and that MRD negativity itself was associated with long-term survival.[84] A summary of the trials evaluating maintenance therapy in MM is listed in Table 2.

Thalidomide

Although some studies have shown that maintenance treatment with thalidomide improves outcomes, its high rate of adverse events has precluded it from routine use.[17–19] A randomized phase III trial of thalidomide and prednisone as maintenance therapy after ASCT by the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial showed that maintenance therapy with thalidomide–prednisone after ASCT improved the duration of disease control, but without OS benefit.[20] However, patients allocated to thalidomide–prednisone experienced lower health-related quality of life scores for global, cognitive, role function domains, and for many symptoms, including dyspnea, constipation, thirst, swelling in the legs, numbness, dry mouth, and balance problems.[20] This has also been observed in real-world clinical practice where continuous thalidomide is generally poorly-tolerated because of adverse symptoms. Of note, some studies have suggested that patients with high-risk MM may actually have worse response rates with thalidomide therapy.[17,19,85]

Lenalidomide

Lenalidomide has gained extensive evaluation as maintenance therapy in view of its relatively tolerable side effect profile as compared with thalidomide. Multiple randomized controlled trials (RCTs) have shown improved outcomes with lenalidomide maintenance therapy and it is currently used routinely as maintenance therapy post-ASCT.[21,22]

The IFM group conducted a phase III, placebo-controlled trial to investigate the efficacy of lenalidomide maintenance therapy after ASCT. Patients were randomly assigned to maintenance therapy with either lenalidomide or placebo until relapse. This trial showed that lenalidomide maintenance therapy improved median PFS (41 months, *versus* 23 months; $p < 0.001$), but with no OS benefit at 4 years.[21]

The Cancer and Leukemia Group B (CALGB) study which randomly assigned patients after ASCT to lenalidomide or placebo until disease progression, showed improved PFS in the lenalidomide group [46 months *versus* 27 months ($p < 0.001$)], which translated into improved OS at 3 years (88% *versus* 80%).[22]

The GIMEMA study carried out by Palumbo and colleagues was an open-label, randomized, phase III study that included the evaluation of lenalidomide maintenance therapy until disease progression or unacceptable side effects *versus* no maintenance therapy in patients with newly diagnosed MM.[14] This study showed that maintenance therapy with lenalidomide, when compared with no maintenance, was associated with a significantly reduced risk of disease progression or death (HR 0.47) and the most appropriate treatment strategy in this trial (induction therapy followed by high-dose melphalan and lenalidomide maintenance) was associated with a 5-year rate of PFS from the time of diagnosis of approximately 48% and an OS rate of 78% among all patients.[14]

A meta-analysis combining the above three RCTs showed a significant OS benefit and confirmed the PFS benefit with lenalidomide maintenance after ASCT in patients with newly diagnosed MM when compared with placebo or observation.[86] However, patients with ISS stage III and patients with high-risk cytogenetics did not experience an OS benefit.[86]

Patients with a VGPR or better after ASCT had more favorable outcomes with lenalidomide maintenance and patients who received lenalidomide-based induction therapy had the most favorable OS benefit.[86] There was an increased risk of hematologic and solid tumor secondary primary malignancies (SPM) with lenalidomide maintenance when compared with placebo or observation (5.3–5.8% in the lenalidomide group).[86] However, the overall risk of developing MM disease progression was greater than that of developing an SPM.[86] The

Table 2. Maintenance therapy.

Author (trial/group)	Patient population (thalidomide versus none)	Induction therapy	Treatment regimen	PFS or EFS (maintenance versus none)	OS (maintenance versus none)
Thalidomide maintenance					
Attal et al. (IFM)[17]	597 patients (201 in arm C versus 200 in arm A versus 196 in arm B)	VAD×3–4+double ASCT	Arm A: no maintenance Arm B: pamidronate Arm C: pamidronate + thalidomide (50–400 mg)	EFS: 52% (arm C) versus 36% (arm A) versus 37% (arm B) (p < 0.009)	4-year OS: 87% (arm C) versus 77% (arm A) versus 74% (arm B) (p < 0.04)
Spencer et al.[18]	243 patients (114 versus 129)	Physician's discretion + ASCT	Thalidomide 100–200 mg daily for a maximum of 12 months + prednisolone (50 mg) alternate days (both arms) until disease progression	3-year PFS: 42% and 23% (p < 0.001)	3-year OS: 86% versus 75% (p = 0.004)
Morgan et al. (Myeloma IX)[19]	818 patients (408 versus 410)	Intensive (+ ASCT) or nonintensive pathway	Thalidomide 50–100 mg daily until disease progression	Median PFS: 23 versus 15 months (p < 0.001)	Median OS: No difference (p = 0.40)
Stewart et al. (Myeloma 10)[20]	332 patients (166 versus 166)	Physician's discretion (without thalidomide or lenalidomide) + ASCT	Thalidomide 100–200 daily + prednisone 25–50 mg on alternate days for 4 years or until disease progression	4-year PFS: 32% versus 14% (p < 0.0001)	4-year OS: 68% versus 60% (p = 0.18)
Lenalidomide maintenance					
Attal et al. (IFM)[21]	614 patients (307 versus 307)	Physician's discretion + ASCT + lenalidomide consolidation × 2	Lenalidomide 10–15 mg daily until disease progression	Median PFS: 41 months versus 23 months (p < 0.001)	4-year OS: no OS benefit (73% versus 75%)
Carthy et al. (CALGB)[22]	460 patients (231 versus 229)	Physician's discretion + ASCT	Lenalidomide 10 mg daily until disease progression	Median PFS: 46 months versus 27 months (p < 0.001)	3-year OS: 88% versus 80%. (hazard ratio, 0.62; CI 95% 0.40–0.95)
Palumbo et al. (GIMEMA)[14]	251 patients 126 (versus 125)	RD × 4 + (double ASCT versus MPR)	Lenalidomide 10 mg daily d1–21 until disease progression	41.9 months versus 21.6 months (p < 0.001)	3-year OS: 88% versus 79.2% (p = 0.14)
Jackson et al. (Myeloma XI)[23]	1971 patients (1137 versus 834)	Intensive (+ASCT) or nonintensive treatment	Lenalidomide 10 mg daily d1–21 until disease progression	Median PFS: 39 months versus 20 months (p < 0.0001)	3-year OS: 78.6% versus 75.8% (p = 0.15)
Bortezomib maintenance					
Sonneveld et al. (HOVON-65/ GMMG-HD4)[24]	499 patients (229 in bortezomib arm versus 270 in thalidomide arm)	VAD or PAD + ASCT	Bortezomib 1.3 mg/m² every 2 weeks for 2 years in PAD group (versus thalidomide in VAD group)	Median PFS: 35 months versus 28 months (p = 0.002)	Median OS: not reached at 66 months in both arms
Ixazomib maintenance					
Dimopoulos et al. (Tourmaline-MM3)[25]	656 patients (395 versus 261)	Physician's discretion (must include PI or IMiD) + ASCT	Ixazomib 3–4 mg d1,8, and 15 for 2 years	Median PFS: 26.5 versus 21.3 months (p = 0.0023)	OS: Inconclusive due to insufficient events

ASCT, Autologous Stem-cell Transplant; CALGB, Cancer and Leukemia Group B; EFS, event-free survival; IFM, Inter-Groupe Francophone du Myelome; IMiD, immunomodulatory drug; OS, overall survival; PAD, bortezomib–doxorubicin–dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; VAD, vincristine–doxorubicin–dexamethasone.

mean duration of lenalidomide maintenance was 2 years in the IFM study, 2.5 years for the CALGB study and 3 years for the GIMEMA study.[86] Another systematic review and network meta-analysis showed a HR in favor of maintenance therapy and by OS analysis, and lenalidomide was identified as the best option.[87]

Following these studies, another recently published study, the Myeloma XI trial showed that lenalidomide maintenance therapy significantly improved PFS in patients with newly diagnosed MM when compared with observation (median PFS 39 *versus* 20 months), but with no OS benefit.[23] This trial included both transplant-eligible and ineligible patients.[23] A prespecified subgroup analysis suggested that continuous lenalidomide improved OS in transplant-eligible patients but not in transplant-ineligible patients.[23] In contrast with the previous meta-analysis, the Myeloma XI trial demonstrated improved PFS with lenalidomide maintenance *versus* observation in patients with high-risk cytogenetics.[23]

Bortezomib

With the meta-analysis previously showing that lenalidomide does not have OS benefit for high-risk patients, some centers have been using bortezomib maintenance for high-risk patients because previous studies have shown that it was effective in them.[24,88,89]

The IFM 2005-01 phase III trial showed that bortezomib plus dexamethasone was effective in high-risk patients, including patients with ISS stage III disease and high-risk cytogenetic abnormalities.[88]

The initial report of the Dutch–Belgian Cooperative Trial Group for Hematology Oncology Group-65/German-speaking Myeloma Multicenter Group-HD4 (HOVON-65/GMMG-HD4) phase III trial comparing vincristine, doxorubicin, and dexamethasone (VAD) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by high-dose melphalan and ASCT, and subsequent maintenance therapy with thalidomide (VAD) or bortezomib (PAD) for 2 years, showed that bortezomib resulted in a superior outcome in patients with increased serum creatinine.[24] In patients with del(17p13)[90] and del(13q14), the bortezomib arm had significantly better outcomes than the comparison arm.[24] In addition, the bortezomib arm

achieved better results in patients with t(4;14), although it did not reach statistical significance.[24] The long-term results published in 2018 showed similar results.[89] Bortezomib use was associated with improved outcomes in renal impairment and the effect of del(17p13) was abrogated in the bortezomib arm.[89] With regard to t(4;14), similarly, patients with the bortezomib arm showed improved OS compared with the comparison group, but the negative effect was not fully abrogated.[89] However, cytotoxic agents were used as the induction regimen, making the applicability of this result questionable.[89]

Ixazomib

Because bortezomib has to be administered parenterally, ixazomib, an oral PI is, in particular, an attractive maintenance therapy. The recently published phase III Tourmaline–MM3 trial showed that maintenance therapy with ixazomib significantly prolonged PFS following ASCT in newly diagnosed MM patients with a 28% reduction in the risk of progression/death with ixazomib *versus* placebo (median 26.5 *versus* 21.3 months).[25] An important finding is that the PFS benefit was seen across all subgroups, including patients with ISS stage III (HR 0.661), high-risk cytogenetics (HR 0.625), PI-exposed (HR 0.750), and PI-naïve (HR 0.497) patients. It was shown to be well tolerated with a low rate of discontinuation.[25]

Salvage ASCT

For transplant-eligible patients who do not receive upfront ASCT, ASCT as part of salvage therapy is highly recommended.[91] Studies have shown that salvage ASCT after relapse from first ASCT is a feasible option,[92,93] especially in patients who had a TTP of at least 12–18 months after their first ASCT.[91,93] The long-term follow-up results of the British Society of Bone Marrow Transplantation/UK Myeloma Forum (BSBMT/UKMF) Myeloma X Relapse (Intensive) trial supported the benefit of salvage ASCT, including after second relapse.[92] Of note, the benefit of salvage ASCT was reduced in high-risk cytogenetics group.[92] With the development of newer potent novel agents and Chimeric Antigen Receptor (CAR) T-cell therapy for relapsed/refractory MM, a randomized trial is required to evaluate the role of salvage ASCT.

A phase III randomized controlled multicenter trial from the German-speaking Myeloma Multicenter Group (GMMG), the ReLApsE trial, compared standard continuous Rd (arm A) with Rd re-induction, salvage ASCT and lenalidomide (R) maintenance (arm B) in an intention-to-treat analyses and showed that there were no significant differences in median PFS (18.8 months in arm A *versus* 20.7 months in arm B; HR 0.87; CI 95% 0.65–1.16; *p* = 0.34) and OS (62.7 months in arm A *versus* not reached in arm B; HR 0.81; CI 95% 0.52–1.28; *p* = 0.37).[94] One important caveat was that 29.5% of patients in arm B did not receive the planned ASCT.[94] An exploratory landmark performed achieved [median interval from randomization to HDT/Rd cycle 5: 117/122 days; *n* = 103(B)/114(A)] showed a trend toward superior PFS (23.3 *versus* 20.1 months; HR 0.74; *p* = 0.09) and significantly superior OS (not reached *versus* 57 months; HR 0.56; *p* = 0.046) in arm B *versus* A.[94] A subgroup analysis evaluating the benefit of PFS, OS, or both from ASCT showed improved outcomes in patients with front-line ASCT and patients with low risk according to Lactate Dehydrogenase (LDH), cytogenetics, and R-ISS.[95]

Allogeneic stem-cell transplantation

Studies have shown conflicting results regarding the benefit of allo-SCT in MM. The IFM 99-03 and 99-04,[96] PETHEMA,[97] Hovon,[98] and BMT–CTN[99] studies showed no significant difference in survival between tandem autologous-allogeneic SCT and ASCT only. The Italian[100,101] and EBMT[102,103] studies showed that OS were improved in the tandem autologous-allogeneic SCT groups. A meta-analysis of six clinical trials in newly diagnosed MM patients showed that allo-SCT was associated with higher transplant-related mortality and CR rate without improvement in PFS or OS.[104] In view of the conflicting data and availability of potent novel agents today, allo-SCT is only reserved for special circumstances, for example, when there are no other better options in young patients with high-risk disease or as part of prospective clinical trials.

Conclusion

We have come a long way with multiple strategies in incorporating stem-cell transplantation for MM treatment and, to date, it remains a key component in the current MM treatment landscape. With the emerging development of potent novel agents and immunotherapy including CAR-T cell therapy, further prospective clinical trials are required to evaluate the most appropriate treatment strategies when managing MM patients.

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The author(s) declare that there are no conflicts of interest.

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