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REVIEW

# Stem cell transplantation for multiple myeloma: current and future status

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Stem cell transplantation (SCT) has been used in the treatment of multiple myeloma (MM) for decades and has become a standard of care for newly diagnosed MM patients. However, several important questions remain regarding the optimal use of SCT, particularly in light of the many recent advances in the treatment of MM. Bortezomib-based therapy or, in some cases, lenalidomide-based therapy should be considered as an induction therapy in transplantation-eligible patients. Efforts to improve upon the efficacy and safety of standard transplantation regimens (that is, high-dose melphalan) are also underway. Most published studies on the use of tandem autologous SCT were conducted before the advent of novel agents, such as thalidomide, lenalidomide and bortezomib, making it difficult to establish the current role of tandem SCT. Allogeneic SCT continues to be evaluated in clinical trials, and may have an important role in the treatment of transplantation-eligible patients with suitable donors. Post-transplantation consolidation and maintenance therapy using novel agents should be considered to improve outcomes in patients who fail to achieve a complete response following SCT. Patients in remission should be advised that continued therapy has been shown to prolong remission, improve quality of life and extend survival. Additional data on the optimal approach to post-transplantation therapy are needed. New strategies in development aimed at improving patient selection, safety and efficacy of SCT are likely to improve future outcomes.

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**Keywords:** autologous stem cell transplantation; allogeneic stem cell transplantation; multiple myeloma; melphalan

## INTRODUCTION

It has now been more than 25 years since McElwain and Powles[1,2] demonstrated the clinical impact of melphalan dose on disease response in patients with relapsed and refractory multiple myeloma (MM). Shortly thereafter, Barlogie *et al.*[3,4] showed that the myelosuppressive effects of high-dose melphalan could be attenuated with the use of autologous bone marrow. Since then, significant advances have been made in both intensive and non-intensive MM therapy.

High-dose chemotherapy with autologous stem cell transplantation (ASCT) was first explored as a consolidation therapy in patients with newly diagnosed MM in the early 1990s.[5] In 45 patients in remission within 1 year of initial therapy, ASCT increased the complete response (CR) rate from 5 to 45%; among 27 patients with primary resistance within 1 year of initial therapy, 19 (70%) responded to ASCT.[5] Although most phase III trials comparing high-dose chemotherapy with conventional therapy demonstrated a progression-free survival (PFS) benefit for the high-dose therapy arm, only two studies showed an overall survival (OS) benefit after a standard induction regimen with steroids and alkylators, or an anthracycline.[6,7]

The timing of high-dose therapy with ASCT needs to be re-examined with the advent of new induction therapies containing lenalidomide, thalidomide and/or bortezomib. This article will summarize the results of ongoing and recently published clinical trials and describe how they have affected current ASCT recommendations.

## OPTIMAL INDUCTION TREATMENT BEFORE SCT

Response before ASCT is associated with improved outcomes following ASCT, but the optimal type and duration of induction therapy has not been well defined.[8] Macro *et al.*[9] reported the results of a randomized trial comparing two induction regimens: thalidomide plus dexamethasone with vincristine, doxorubicin and dexamethasone. Despite a higher pre-ASCT response to thalidomide plus dexamethasone (very good partial response (VGPR) or better: 34.7% versus 12.6% for vincristine, doxorubicin and dexamethasone), both groups had similar response rates after ASCT (VGPR or better: 44% versus 41.7%). In contrast, three randomized trials have demonstrated that bortezomib-based induction therapy improves response rates and PFS following ASCT,[7,10,11] although only one of them showed an improvement in OS.[11] This could be due to the beneficial effects of novel agents when used as salvage therapy. The results of these trials are summarized in Table 1.[7,10,11]

Lenalidomide-based induction therapy is also an option and it has been used primarily in North America.[12] In a recent retrospective analysis of data from the E4A03 trial, patients aged $<65$ years, who underwent early ASCT after four cycles of lenalidomide plus dexamethasone had a 3-year OS rate of 94% compared with a rate of 78% for those who continued protocol therapy.[13] This led to the inclusion of lenalidomide-based induction regimens in the National Comprehensive Cancer Network guidelines.[14]

Further intensification of the induction regimen has been shown to improve response rates before ASCT,[15,16] but the impact

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**Table 1.** Phase III trials evaluating bortezomib-based induction therapy

| *Reference* | *N* | *Treatment* | *CR/nCR after all therapy* | *PFS* | *3-year OS* | *Significance* |
|---|---|---|---|---|---|---|
| Cavo *et al.*[7] | 474 | BTD vs TD | 58% vs 41% | 3-year: 68% vs 56% | 86% vs 84% | $P<0.05$ for response and PFS |
| Harousseau *et al.*[10] | 482 | BD vs VAD | 40% vs 23% | Median: 36 vs 29.7 months | 81% vs 77% | $P<0.05$ for response |
| Sonneveld *et al.*[11] | 613 | PAD vs VAD | 50% vs 38% | 3-year: 48% vs 42% | 78% vs 71% | $P<0.05$ for PFS and OS |

Abbreviations: A, doxorubicin; B, bortezomib; CR, complete response; D, dexamethasone; nCR, near CR; OS, overall survival; PFS, progression-free survival; T, thalidomide; V, vincristine.

on OS has not been established. Richardson *et al.*[15] reported transplantation outcomes in 28 patients who received induction therapy with lenalidomide, bortezomib and dexamethasone. This combination was associated with a high response rate (VGPR or better: 67%). Estimated 18-month PFS and OS were 75% and 97%, respectively. More intense four-drug combinations, such as the combination of bortezomib, dexamethasone, cyclophosphamide and lenalidomide, have been associated with higher toxicity rates when compared with three-drug combinations, without significant increases in response rates.[16]

For transplantation-eligible patients, a bortezomib-based induction regimen is associated with improved disease control post transplantation, and should be considered the standard of care. Lenalidomide plus dexamethasone is a reasonable alternative in patients with low-risk disease.[14]

## ROLE OF ASCT

Before the advent of immunomodulatory drugs and proteasome inhibitors, the CR rates after induction therapy were $<10\%$.[5] Thus, the rationale to proceed to high-dose therapy with ASCT was to increase the depth of response and the number of patients who achieve a CR.[17] This rationale was supported by retrospective analyses confirming CR as an important surrogate endpoint for survival and long-term disease control,[17] and subgroup analyses of randomized controlled trials examining the effect of response on survival.[6,18] To increase dose-intensity, Barlogie *et al.*[19] showed the feasibility of tandem ASCTs using melphalan 200 mg/m$^2$ for the first transplantation and either melphalan 200 mg/m$^2$ or melphalan plus total body irradiation (TBI) for the second transplantation. Of 123 patients enrolled in this trial, 76% completed a second ASCT. Tandem ASCT was associated with a 40% CR rate and a median event-free survival (EFS) of 49 months. Attal *et al.*[20] reported on 399 patients aged $<60$ years randomized to either single or tandem ASCT, and showed that tandem transplantation significantly improved 7-year EFS and OS. Cavo *et al.*[21] reported on 321 patients randomly assigned to receive either single or tandem courses of high-dose therapy with stem cell support. Patients in the tandem arm were more likely to achieve at least a near CR (33% versus 47%) and had prolonged EFS (median, 23 versus 35 months); however, no survival benefit was observed. Subgroup analyses of both trials suggested that the benefits of a second ASCT are experienced mainly by patients who achieved less than a VGPR after the first transplantation. Neither of these studies included induction regimens that contained immunomodulatory drugs or proteasome inhibitors; therefore, as with the initial randomized trials comparing single transplantation with chemotherapy, they are not as relevant today as when they were originally published.

The recent experience with Total Therapy II and Total Therapy III trials have underscored the feasibility and efficacy of intensive induction, followed by consolidation and maintenance therapy as a strategy for obtaining high rates of CR and durable remissions in patients with standard-risk cytogenetic abnormalities.[22,23]

## IMPROVING ON HIGH-DOSE MELPHALAN

Several studies have been performed with the aim of identifying more effective regimens than single-agent high-dose melphalan. Only one randomized controlled trial has been reported; in this trial, single-agent melphalan was compared with melphalan plus TBI.[24] The outcomes after melphalan plus TBI were comparable to those achieved with melphalan alone in terms of response and EFS, but OS was inferior with the addition of TBI. In a phase I study, the novel targeted radiotherapeutic $^{166}$Ho-DOTMP (Holmium-166 combined with the bone-seeking tetraphosphonate DOTMP) was given to high-risk MM patients before high-dose melphalan and ASCT.[25] Significant renal and bladder toxicity occurred at the highest doses, but response rates were encouraging (CR in 29 of 83 patients (35%)). A similar approach was developed using Samarium-153 linked to a different bone-seeking agent (ethylenediamine tetra(methylene phosphonic acid)) and combined with high-dose melphalan. This lower-energy isotope was associated with no significant renal or bladder toxicity, and response was observed in 17 of the 18 patients (94%), including 5 patients who achieved CR (28%).[26] Phase I and II trials have combined high-dose melphalan with other drugs, including busulfan or idarubicin, with no apparent significant improvements in outcomes.[27,28] More recently, bortezomib was combined with high-dose melphalan followed by ASCT in a phase II study.[29] The regimen was well tolerated and appeared to improve response rates when compared with historical controls (CR rate: 35% versus 11% with high-dose melphalan only; $P=0.001$).

## POST-TRANSPLANTATION THERAPIES

Despite intensive induction and tandem transplantation consolidation therapy, myeloma recurrence occurs almost universally in the absence of post-transplantation therapy. Interferon was the first agent extensively studied in the context of post-transplantation maintenance and studies produced conflicting results. Today, interferon is rarely used in this setting because of adverse events and poor tolerability.[30] Thalidomide has been studied in several randomized trials and has been the only agent to conclusively increase PFS and OS when given as maintenance therapy post ASCT (Table 2).[22,31–36] On the other hand, the side-effect profile of thalidomide has hindered its adoption as long-term maintenance therapy.

Lenalidomide, with its better side-effect profile compared with thalidomide, has also been explored in the context of post-transplantation maintenance therapy. Results from two randomized trials using lenalidomide have been recently reported.[37,38] In the IFM-2005-02 trial,[37] 614 patients were randomized to maintenance therapy with placebo or lenalidomide (10 mg daily for the first 3 months, followed by 15 mg daily if tolerated) after receiving 2 months of lenalidomide consolidation therapy. With a median follow-up of 30 months, PFS improved significantly with lenalidomide (median 41 versus 23 months; hazard ratio $=0.50$, $P<0.001$) with similar findings for EFS. In the CALGB 100104 trial,[38] patients who had undergone a single ASCT were randomized to

**Table 2.** Phase III trials evaluating thalidomide maintenance therapy after autologous stem cell transplantation

| *Reference* | *Treatment* | *N* | *⩾VGPR* | *EFS/PFS* | *OS* | *Significance* |
|---|---|---|---|---|---|---|
| Stewart *et al.*[31] | T+Pred vs none | 332 | NR | 4-year PFS: 32% vs 14% | 4-year: 68% vs 60% | Significant for PFS |
| Spencer *et al.*[32] | T+Pred vs Pred[a] | 243 | 63% vs 40% | 3-year PFS: 42% vs 23% | 3-year: 86% vs 75% | $P<0.05$ for PFS and OS |
| Attal *et al.*[33] | T+Pam vs Pam vs none | 597 | 67% vs 57% vs 55% | 3-year EFS: 52% vs 37% vs 36% | 4-year: 87% vs 74% vs 77% | $P<0.05$ for all endpoints favoring T[b] |
| Lokhorst *et al.*[34] | T vs IFN | 556 | 66% vs 54% | Median PFS: 34 vs 25 months | Median: 73 vs 60 months | $P<0.05$ for response and PFS |
| Barlogie *et al.*[35] | T+IFN+D vs IFN+D[c] | 668 | NR | 5-year EFS: 56% vs 45% | 8-year: 67% vs 65% | $P<0.05$ for EFS[d] |

Abbreviations: D, dexamethasone; EFS, event-free survival; IFN, interferon; NR, not reported; OS, overall survival; Pam, pamidronate; PFS, progression-free survival; Pred, prednisone/prednisolone; T, thalidomide; VGPR, very good partial response.
[a]T was given for 12 months only; Pred was given indefinitely.
[b]After extended follow-up (median 5.7 years), the difference between groups in terms of OS was no longer significant.[22]
[c]Treatment was given as part of Total Therapy II, in which patients were randomized to standard therapy or standard therapy plus T at all phases of treatment, including maintenance.
[d]After extended follow-up (median 7.2 years), a significant benefit in OS emerged favoring T.[22,36]

placebo or lenalidomide maintenance therapy (10 mg daily (range 5–15 mg)). Median time-to-progression was significantly improved in patients receiving lenalidomide maintenance (46 versus 27 months, hazard ratio = 0.48, $P<0.001$). With a median follow-up of 34 months, lenalidomide improved median OS (35 versus 53 months; hazard ratio = 0.62, $P=0.03$), despite the crossover design. In both trials, an increased risk of second primary malignancies was observed in the lenalidomide group; overall, the reported incidence of second primary malignancies in clinical trials in newly diagnosed patients has been higher with lenalidomide (7%) than in controls (1.8%).[39] The second primary malignancies observed in patients receiving lenalidomide maintenance therapy include hematologic malignancies (primarily acute myelogenous leukemia, myelodysplastic syndromes and Hodgkin disease) and solid tumors.[39]

Bortezomib maintenance has also been shown to reduce the risk of relapse. Sonneveld *et al.*[11] reported outcomes for 626 patients randomized to bortezomib-based induction therapy followed by post-transplantation bortezomib therapy every other week for 2 years, or thalidomide-based induction therapy and maintenance. Bortezomib-based therapy was associated with a higher response rate (VGPR or better: 60% versus 40%); on multivariate analysis, bortezomib therapy was also associated with improved PFS ($P=0.037$) and OS (hazard ratio = 0.74; $P=0.048$). Unfortunately, as use of bortezomib was limited to only one of the treatment groups, it is impossible to separate the benefits of bortezomib induction from maintenance in this trial.

In summary, the novel agents thalidomide, lenalidomide and bortezomib have been shown to enhance disease control when given after ASCT in patients with newly diagnosed MM. The increased risk of second primary malignancies seen after lenalidomide requires further follow-up. Although the data to date suggest that most patients may benefit from post-transplantation therapies, particularly if they still have evidence of residual disease, the optimal agent, timing and duration of post-transplantation therapy remain to be defined. Thus, continued clinical trials addressing these issues will be essential.

## ROLE OF ALLOGENEIC SCT IN MM

The role of allogeneic SCT (alloSCT) has been the subject of considerable controversy due to conflicting results from various clinical trials (Table 3).[40–45] In a study conducted by the Blood and Marrow Transplant Clinical Trials Network, 625 patients with standard-risk MM were assigned to receive either tandem ASCT using melphalan 200 mg/m$^2$ ($n=436$) or one ASCT followed by alloSCT conditioned with fludarabine and 2 Gy of TBI ($n=189$).[43] The 3-year PFS rate was 46% in the tandem ASCT group and 43% for the ASCT/alloSCT group ($P=0.67$). The 3-year OS rate was also comparable in both groups: 80% for the tandem ASCT group and 77% for the ASCT–alloSCT group ($P=0.19$). In a cohort of 85 high-risk patients treated in the same trial, the 3-year PFS rate was 33% and 40% ($P=0.74$), and the 3-year OS was 67% and 59% for the tandem ASCT and ASCT/alloSCT groups, respectively ($P=0.46$).[44] This trial allowed patient enrollment after human leukocyte antigen typing had been performed, which potentially could have introduced a referral bias. Conflicting results were reported from a prospective trial conducted by the European Group for Bone Marrow Transplantation. In this study, 357 patients were assigned to ASCT (single or double) or tandem ASCT/reduced-intensity alloSCT, depending on the availability of a human leukocyte antigen-matched donor.[46] Preparative regimens were identical to those used in the Blood and Marrow Transplant Clinical Trials Network trial. With a median follow-up of 60 months, the 5-year PFS was 35% for the ASCT/alloSCT group and 18% for the tandem ASCT group $P=0.001$); the 5-year OS was 65% and 58%, respectively ($P=0.047$). One possible explanation for the discrepancy in these results from the Blood and Marrow Transplant Clinical Trials Network trial is the longer follow-up time (nearly 3 more years) in the European Group for Bone Marrow Transplantation trial.

Allogeneic transplantation as part of frontline therapy should continue to be explored in the context of clinical trials. Young patients with high-risk disease and suboptimal response to induction therapy should be considered for this approach, if an optimal donor is identified. In patients with low-risk disease and low tumor bulk, allografting is probably better used as salvage therapy. Optimal intensity of the conditioning regimen remains to be determined.[45,47]

## SUMMARY

Outside of the context of a clinical trial, optimal induction therapy would be with either a bortezomib- or lenalidomide-based combination. In patients with high-risk disease, induction therapy with dexamethasone plus bortezomib, lenalidomide or thalidomide should be considered the treatment of choice, if patients have no specific contraindication to these agents. The optimal duration of induction therapy has not been established, but most experts recommend between four and six cycles of induction before proceeding to stem cell collection and consolidation with high-dose therapy.[48]

Post-transplantation therapies should now be routinely considered for all patients failing to achieve a CR to initial induction and consolidation regimens. Patients who have achieved a CR should be advised that the available evidence suggests that continued therapy with thalidomide, lenalidomide or bortezomib may prolong remission and improve survival. However, whether patients treated pre-emptively at the sign of first relapse could have the same degree of benefit has not been determined. In the

**Table 3.** Trials comparing outcomes following tandem ASCT with tandem ASCT/alloSCT in MM

| *Reference* | *Treatment* | *N* | *Response* | *EFS/PFS* | *OS* | *Significance* |
|---|---|---|---|---|---|---|
| IFM 99-03 and IFM 99-04[40] | ASCT–ASCT (MEL 200) vs ASCT/alloSCT (RIC) | 284 High-risk | NR | Median EFS: 35 vs 31.7 months | Median OS: 47.2 vs 35 months | No difference in EFS; nonsignificant trend toward improved OS favoring ASCT–ASCT ($P=0.07$) |
| Bruno *et al.*[41] | ASCT–ASCT (MEL 200) vs ASCT/alloSCT (TBI) | 162 NDMM | CR: 26% vs 55% | Median EFS: 29 vs 35 months | Median OS: 54 vs 80 months | $P=0.02$ for EFS and $P=0.01$ for OS favoring ASCT/alloSCT |
| PETHEMA[42] | ASCT–ASCT (MEL 200) vs ASCT/alloSCT (RIC) | 110 With <nCR after first SCT | CR: 11% vs 40% | Median PFS: not reached vs 31 months | — | $P=0.01$ for CR; nonsignificant trend toward improved PFS favoring ASCT/alloSCT ($P=0.08$) |
| BMT-CTN 0102[43] | ASCT–ASCT (MEL 200) vs ASCT/alloSCT (TBI) | 625 Standard-risk | NR | 3-year PFS: 46% vs 43% | 3-year OS: 80% vs 77% | No significant difference in PFS or OS |
| BMT-CTN 0102[44] | ASCT–ASCT (MEL 200) vs ASCT/alloSCT (TBI) | 85 High-risk | NR | 3-year PFS: 33% vs 40% | 3-year OS: 67% vs 59% | No significant difference in PFS or OS |

Abbreviations: alloSCT, allogeneic SCT; ASCT, autologous SCT; CR, complete response; EFS, event-free survival; MEL 200, melphalan 200 mg/m$^2$; nCR, near CR; NDMM, newly diagnosed multiple myeloma; NR, not reported; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; TBI, total body irradiation.

meantime, it is reasonable to observe patients with low-risk disease who have achieved a CR after induction and consolidation, and intervene at the time of disease progression.

Identification of high-risk MM as defined by cytogenetics and gene expression profiling has allowed investigators to develop risk-stratified strategies; these strategies need to be tested in prospective clinical trials before they can be considered standard.[49] Improving transplantation outcomes over the next 5 years will require the exploration of novel strategies aimed at addressing the following issues:

- Reducing the morbidity associated with high-dose therapy
  - reducing symptom burden by using anti-cytokine approaches (for example, anti-interleukin-6 monoclonal antibody)
  - enhancing immune-recovery (for example, using megadoses of stem cells)
  - identifying patients at high-risk for gastrointestinal toxicity and adjusting the dose of melphalan accordingly
  - using cytoprotective drugs, such as palifermin or amifostine
- Improving the efficacy of conditioning regimens
  - assessment of novel conditioning regimens
- Improving post-transplantation therapy
  - use of combination therapies for patients with high-risk disease
  - use of immunotherapy (for example, vaccines and adoptive immunotherapy) to prevent relapse
- Improving the detection of minimal residual disease

Continued support and participation in clinical trials and continued global collaborative efforts will make long-term disease control for most patients with MM an achievable goal within the next 5–10 years.

## CONFLICT OF INTEREST

WB has participated in a speakers bureau and advisory board, and has received clinical research support from Celgene Corporation. He has also participated in an advisory board and has received clinical research support from Millennium and Onyx Pharmaceuticals. WB has also received grant support from AstraZeneca and Acetylon Pharmaceuticals. SG has had a consultancy role and received honoraria from Biokine Therapeutics, Miltenyi Biotech, Onyx, Celgene Corporation and Sanofi; he has also received lecture fees and grants from Celgene Corporation.

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