The Role of Transplant in Multiple Myeloma

Matthew Mei, MD,a,b and George Somlo, MD,a,b

Abstract
Over the past decades significant therapeutic advances have been made in the treatment of multiple myeloma (MM). A population-based study of 45,595 patients showed substantial incremental increases in myeloma-specific survival in patients younger than 80 years treated between 1973 and 2009. Depth of response to therapy has long been associated with improved long-term outcomes. Autologous stem cell transplantation (ASCT) was previously the only modality capable of inducing a very good partial response (VGPR) or complete response (CR) in a substantial proportion of patients. The introduction of 2 classes of novel agents, immunomodulatory drugs and proteasome inhibitors, resulted in induction regimens that achieve VGPR rates exceeding 60% even before transplant, thus challenging the role of ASCT. Allogeneic stem cell transplantation (allo-SCT) has also been tested in patients with MM; however, its current role remains undefined given the high rates of transplant-related mortality and chronic graft-versus-host disease. Posttransplant consolidation and maintenance strategies have further improved progression-free and overall survivals. This article discusses the current roles of ASCT, allo-SCT, and consolidation and maintenance therapies in the management of MM.

(J Natl Compr Canc Netw 2014;12:1131–1138)

Over the past decades significant therapeutic advances have been made in the treatment of multiple myeloma (MM). A population-based study of 45,595 patients showed substantial incremental increases in myeloma-specific survival in patients younger than 80 years treated between 1973 and 2009.1 Depth of response to therapy has long been associated with improved long-term outcomes.2 Autologous stem cell transplantation (ASCT) was previously the only modality capable of inducing a very good partial response (VGPR) or complete response (CR) in a substantial proportion of patients.3,4 The introduction of 2 classes of novel agents, immunomodulatory drugs (IMiDs) and proteasome inhibitors, resulted in induction regimens that achieve VGPR rates exceeding 60% even before transplant,5,6 thus challenging the role of ASCT. Allogeneic stem cell transplantation (allo-SCT) has also been tested in patients with MM; however, its current role remains undefined given the high rates of transplant-related mortality (TRM) and chronic graft-versus-host disease (GVHD). Posttransplant consolidation and maintenance strategies have further improved progression-free (PFS) and overall survival (OS). This article discusses the current roles of ASCT, allo-SCT, and consolidation and maintenance therapies in the management of MM.

Autologous Stem Cell Transplantation

Single Autologous Transplantation
After early-phase trials established the viability of ASCT, the Intergroupe Francophone du Myélome (IFM) reported the results of a phase III trial randomizing patients to an anthracycline-based induction regimen followed by either ASCT or further chemotherapy, and found event-free survival (EFS) and OS to be significantly prolonged with ASCT.7 A second randomized trial comparing ASCT and continued chemotherapy confirmed superior OS with ASCT (54.1 vs 42.3 months), with patients having elevated β2-microglobulin levels experiencing the most benefit.8 Subsequent trials have confirmed that ASCT signifi-
significantly deepens the response obtained with primary therapy, and ASCT has become standard of care for patients who are transplant-eligible from the standpoint of performance status and organ function. A recent retrospective analysis of 1038 patients treated at the Mayo Clinic between 2001 and 2010 also reported superior OS after ASCT; the median OS has not been reached, compared with 4.9 years for those not receiving ASCT ($P<.001$). However, the role of ASCT after modern induction therapy needs further exploration.

**Timing of Transplant**

ASCT can be performed either early after induction therapy or later at disease progression. Fermand et al. compared early and late ASCT and found a similar OS, although the average time without symptoms, treatment, and treatment toxicity was significantly better with early ASCT. A retrospective study of 167 patients who received induction therapy containing at least 1 of 3 novel agents (the IMiDs lenalidomide or thalidomide, or the PI bortezomib) followed by ASCT either within 12 months of diagnosis or later found a higher CR rate in the early ASCT arm but no difference in PFS or OS. The potential benefit of early versus late ASCT was assessed in a trial randomizing patients between 55 and 65 years of age to either conventional chemotherapy alone or chemotherapy followed by ASCT. Within a median follow-up of 120 months, a trend toward increased EFS, but no OS benefit, was observed in the patients undergoing early transplant. Finally, the US Intergroup Trial S9321 found no PFS or OS benefit with early ASCT, although most of the patients who experienced relapse while undergoing chemotherapy confirmed that delayed ASCT had an adverse effect on OS.

**Tandem ASCT**

Tandem ASCT refers to a planned second ASCT occurring within 6 months of the first. The IFM compared tandem versus single ASCT and reported that EFS and OS were significantly prolonged by tandem ASCT. However, multiple issues render the results difficult to apply, including the fact that the conditioning regimen included total body irradiation and outdated induction regimens were used, with a VGPR rate of only 42% even after the first ASCT. Another prospective randomized trial of 321 patients showed improvement in depth of response and EFS, but no improvement in OS; the greatest clinical benefit was seen in patients who did not experience at least a near CR with the first transplant, although the trial was not adequately powered to demonstrate a difference in this subgroup. A meta-analysis of 6 randomized trials comparing tandem versus single ASCT found increased response rates but no consistent OS or EFS benefit; however, significant heterogeneity was seen among the trials analyzed, and one of the “negative” randomized trials was subsequently withdrawn by the authors. Currently, tandem ASCT is preferably considered if a VGPR is not realized after the first ASCT, or in high-risk patients. The 3-arm BMT CTN 0702 trial, which randomized patients to either single ASCT followed by maintenance, single ASCT followed by both PI- and IMiD-containing consolidation therapy and then maintenance, or tandem ASCT followed by maintenance, has just completed accrual and will likely clarify the feasibility and role of tandem ASCT in the modern era (ClinicalTrials.gov identifier: NCT01109004).

**Consolidation/Maintenance Therapy**

Most patients with MM undergoing ASCT will eventually experience progressive disease. Therefore, both consolidation and maintenance strategies have been used to improve disease control and long-term outcomes.

**Consolidation Therapy**

Consolidation refers to therapy administered after ASCT with the objective of deepening the response. Few studies have been designed to specifically assess the role of consolidation. For example, investigators in GIMEMA conducted a phase III trial randomizing patients to induction with bortezomib, thalidomide, and dexamethasone (VTD) or thalidomide and dexamethasone (TD), followed by tandem ASCT and 2 cycles of consolidation identical to the regimens used in induction. Results showed that 30.5% of patients receiving VTD upgraded from less than CR to CR after consolidation compared with 16.7% of patients in the TD arm, and VTD seemed to overcome the adverse prognosis conferred by the presence of (4;14) or del(17p). However, because of the comparison of VTD versus TD, the role of consolidation cannot be separated out within the 2 arms.

The IFM performed a prospective randomized trial of 217 patients, examining VTD induction followed
by single ASCT and 2 consolidation cycles of VTD versus no posttransplant therapy, and found that response improved after consolidation in 24% of patients, and time to progression also increased significantly. More recently, Nooka et al20 showed that consolidation therapy with lenalidomide, bortezomib, and dexamethasone (RVD) after ASCT resulted in an impressive stringent CR rate of 51% and a 3-year OS of 93% at 32 months in high-risk patients.

Single-agent consolidation has also been tested in the post-ASCT setting. The Nordic Myeloma Study Group evaluated bortezomib after ASCT in a randomized phase III trial of 370 patients.21 Up to 20 doses of single-agent bortezomib were administered over 21 weeks. Significant improvement was seen in PFS (27 vs 20 months) and depth of response, but no OS benefit was found. Finally, although the IFM 2005-02 trial was a placebo-controlled trial of post-ASCT maintenance lenalidomide, all patients received 2 cycles of single-agent lenalidomide as consolidation, with the finding that consolidation followed by maintenance lenalidomide improved the quality of response.22 Currently, consolidation therapy has been clearly shown to deepen responses obtained with ASCT, but more data are needed to demonstrate its long-term benefit.

**Maintenance Therapy**

Maintenance therapy is prescribed after ASCT with or without consolidation to prevent disease progression or relapse, although deepening response can be seen, particularly in the first 12 months after ASCT. Several agents have been tried in this setting, including steroids, interferon-alfa, and the novel agents thalidomide, lenalidomide, and bortezomib. The most compelling clinical data thus far are with lenalidomide maintenance.

**Older Agents:** Maintenance therapy with steroids has been tested in myeloma, but the data have primarily been in nontransplant patients. For instance, dexamethasone maintenance in patients receiving melphalan-based induction resulted in increased PFS but did not improve OS,23 and prednisone given every other day at a higher dose was shown to increase PFS and OS compared with a lower-dose regimen,24 but both trials were conducted in patients who did not undergo ASCT. Interferon-alfa has been evaluated as maintenance therapy both in patients who did not receive ASCT and in the post-ASCT setting. A modest but consistent improvement in PFS and OS was seen in multiple trials, but because of its considerable toxicity and in light of the results seen with the novel agents, this agent is no longer recommended.25–27

**Thalidomide:** Thalidomide maintenance has been tested as a single agent and in conjunction with prednisone. Trials have consistently reported improved PFS, but the data regarding OS prolongation is more mixed. For instance, a retrospective review of 112 patients who had received ASCT showed a trend toward improved OS (65.5 vs 44.5 months; P = .09) in the subset of patients who had received thalidomide maintenance,28 and a 3-arm study randomizing patients to placebo, pamidronate, or the combination thalidomide and pamidronate as maintenance therapy post-ASCT showed improved EFS and OS in the combination arm.29 However, post-ASCT thalidomide was not found to improve OS and conferred significant toxicity in a prospective randomized trial of 668 patients.30 Thalidomide in conjunction with prednisone was evaluated in the maintenance setting in a prospective randomized control study of 332 patients and showed improved PFS, at the expense of worse health-related quality of life, and no difference in OS.31 Therefore, although thalidomide is clearly effective in prolonging PFS, the significantly improved tolerability seen with lenalidomide has caused it to largely supplant thalidomide in the maintenance setting.

**Lenalidomide:** Three large randomized trials have evaluated lenalidomide maintenance after single ASCT (Table 1). OS was significantly improved in 2 of these trials, whereas PFS was prolonged in all 3. CALGB 100104 randomized 460 patients younger than 71 years to maintenance lenalidomide versus placebo after ASCT and found that PFS (50 vs 27 months) and OS (not reached vs 73 months) were both significantly improved with lenalidomide. The incidence of second primary malignancies was increased approximately 3-fold with lenalidomide maintenance.32,33

Another placebo-controlled trial featured induction with lenalidomide and dexamethasone followed by a first randomization to either consolidation with melphalan, lenalidomide, and prednisone (MPR) or tandem ASCT, followed by a second randomization to either maintenance lenalidomide or placebo. PFS was significantly increased with
maintenance (41 vs 18 months), as was the 4-year OS rate (75% vs 58%), and second primary malignancies did not seem to be increased with lenalidomide maintenance. In contrast, IFM 2005-02 also assessed the role of maintenance lenalidomide and found a significantly increased 5-year PFS rate (42% vs 18%) but no OS benefit with a median follow-up of 45 months. An updated analysis with a median follow-up of 70 months similarly found no OS benefit.

**Bortezomib:** Data regarding bortezomib maintenance are more limited. The phase III HOVON-65/GMMG-HD4 trial found that maintenance bortezomib resulted in increased median EFS, CR/near CR rates, tolerability, and OS compared with maintenance thalidomide; however, all patients who received bortezomib maintenance were also treated with bortezomib-containing induction therapy, whereas patients receiving thalidomide maintenance received induction with vincristine, doxorubicin, and dexamethasone. Bortezomib has been evaluated in combination with thalidomide as maintenance in a phase III study conducted by the PETHHEMA/GEM group. Patients were randomized to 1 of 3 induction arms, 2 of which featured bortezomib, followed by ASCT, with a second randomization posttransplant to maintenance with interferon-alfa2b, thalidomide, or thalidomide with bortezomib. The thalidomide/bortezomib maintenance arm showed improved PFS but not OS; however, there was no bortezomib-only arm for comparison.

**Salvage ASCT**

In contrast to planned tandem transplant, salvage or late ASCT (ASCT2) is performed when a disease has progressed after prior ASCT. The benefit of this approach is difficult to evaluate given that most of the studies evaluating salvage ASCT are single-institution series. Nonetheless, ASCT2 has been shown to be feasible, with TRM less than 5%. The variable most consistently associated with increased PFS and OS after ASCT2 is the duration of PFS after the first transplant. Clinical benefits of ASCT2 have been reported in patients who experienced a PFS of at least 12 months after ASCT1, with trends toward greater benefit in those with 18 months or greater PFS after ASCT.

**Allo-SCT**

Because most patients with MM will eventually experience disease progression after ASCT, allo-SCT has been the subject of interest because it offers the possibility of graft-versus-tumor effect. Unfortunately, results obtained to date have been mixed at best, because high rates of TRM, including those related to GVHD, present significant obstacles.

### Table 1 Summary of Lenalidomide Maintenance Trials

<table>
<thead>
<tr>
<th>n</th>
<th>Induction</th>
<th>PFS</th>
<th>OS</th>
<th>SPM Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCarthy et al&lt;sup&gt;31&lt;/sup&gt; 460</td>
<td>94% received at least one dose of lenalidomide, thalidomide, or bortezomib during induction</td>
<td>46 vs 27 mo (P&lt;.001)</td>
<td>3-y OS: 88% vs 80% (P=.03)</td>
<td>8% vs 3% during follow-up (P=.008)</td>
</tr>
<tr>
<td>Attal et al&lt;sup&gt;35&lt;/sup&gt; 614</td>
<td>49% received VAD, 45% received bortezomib and dexamethasone</td>
<td>41 vs 23 mo (P&lt;.001)</td>
<td>3-y OS: 80% vs 84% (P=.29)</td>
<td>2.3 per 100 patient-years vs 1.3 (P=.03)</td>
</tr>
<tr>
<td>Gay et al&lt;sup&gt;34&lt;/sup&gt; 402</td>
<td>Lenalidomide and dexamethasone</td>
<td>42.7 vs 17.5 mo (P&lt;.0001)</td>
<td>4-y OS: 80% vs 62% (P=.01)</td>
<td>5 vs 3 total (unknown P value)</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; PFS, progression-free survival; SPM, second primary malignancies; VAD, vincristine, doxorubicin, and dexamethasone.
European Society for Blood and Marrow Transplantation (EBMT) revealed significantly worse survival in patients who underwent allo-SCT, with a 41% TRM at 36 months. Nonetheless, the PFS of patients who were alive at 1 year after transplant was significantly better among those in the allo-SCT arm. Another case-matched comparison of syngeneic transplantation versus ASCT and allo-SCT showed worse survival, with TRM exceeding 40%. Finally, a SWOG trial comparing ASCT versus standard chemotherapy included the option of allo-SCT for patients who were younger than 55 years with an HLA-matched sibling donor; however, this latter arm was closed in light of the prohibitively high 1-year TRM of 53%. Notably, 22% of patients remained progression-free at 7 years, with an apparent plateau in the survival curve. Therefore, although myeloablative allo-SCT may offer a potential cure for some patients, the rates of TRM associated with this treatment are such that NCCN recommends it only be performed in the context of a clinical trial.

**Reduced-Intensity Transplant**

Advances in transplant medicine have made reduced-intensity transplant (RIT) possible, wherein the antitumor effect is primarily provided by the graft-versus-tumor effect (Table 2). Most of the randomized trials have compared ASCT followed by RIT versus tandem ASCT, with patient assignment performed via a genetic randomization. The IFM conducted 2 trials, IFM99-03 and IFM99-04, which enrolled patients with high-risk MM in tandem. Patients with an HLA-matched sibling donor were enrolled on IFM99-03, which was a protocol calling for ASCT followed by RIT, and patients without a matched sibling donor were enrolled on IFM99-04, which specified that patients undergo tandem ASCT. EFS and OS were similar in the 2 trials, but of 42 patients receiving RIT, 18 developed extensive chronic GVHD. In a study of 162 patients with MM who underwent a similar genetic randomization, Bruno et al reported that those undergoing RIT had significantly improved EFS and OS. A follow-up study reported an estimated 5-year OS rate of 64% and a 74% incidence of chronic extensive GVHD.

Three more prospective trials were reported with conflicting outcomes. Reporting on results of the BMT CTN 102 trial, Krishnan et al found no benefit to ASCT followed by RIT compared with tandem ASCT with respect to 3-year PFS or OS in patients with standard-risk MM, and RIT also failed to show benefit for patients with high-risk disease as defined by $\beta_2$-microglobulin level and cytogenetics; in addition, 54% of patients had chronic GVHD at 2 years. These findings were similar to those in the study by Lokhorst et al, who conducted a donor versus no-donor analysis of patients treated in the HOVON-50 study, and reported that the 6-year PFS and OS were similar. The EBMT found improved PFS and OS in patients undergoing RIT compared with tandem transplantation; longer follow-up confirmed that PFS and OS are both significantly improved at 96 months, with a suggestion that the

### Table 2  Clinical Trials Comparing Tandem ASCT Versus ASCT Followed by RIT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>EFS (RIT vs Tandem)</th>
<th>OS (RIT vs Tandem)</th>
<th>TRM</th>
<th>Extensive Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garban et al</td>
<td>284</td>
<td>25 mo in IFM99-03 vs 30 mo in IFM99-04</td>
<td>35 mo in IFM99-03 vs 41 mo in IFM99-04</td>
<td>10.9% in IFM99-03</td>
<td>35.7% in IFM99-03</td>
</tr>
<tr>
<td>Giaccone et al</td>
<td>245</td>
<td>39 vs 33 mo</td>
<td>Not reached vs 5.3 y (P=0.02)</td>
<td>16%</td>
<td>74% (limited and extensive)</td>
</tr>
<tr>
<td>Lokhorst et al</td>
<td>260</td>
<td>6-y PFS: 28% vs 22% (P=0.17)</td>
<td>6-y PFS: 55% in both</td>
<td>16%</td>
<td>55%</td>
</tr>
<tr>
<td>Gahrton et al</td>
<td>357</td>
<td>5-y PFS: 33% vs 18% (P=0.003)</td>
<td>5-y OS: 64% vs 57% (P=0.2)</td>
<td>13% at 36 mo</td>
<td>23%</td>
</tr>
<tr>
<td>Krishnan et al</td>
<td>710</td>
<td>3-y PFS: 46% vs 43% (P=0.671)</td>
<td>3-y OS: 77% vs 80% (P=0.191)</td>
<td>11%</td>
<td>54% (limited and extensive)</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplant; EFS, event-free survival; GVHD, graft-versus-host disease; OS, overall survival; PFS, progression-free survival; RIT, reduced-intensity transplant; TRM, transplant-related mortality.
adverse prognostic factor of del(13) was overcome by allo-SCT.\textsuperscript{55} Thus far, although no trial has found a shorter OS with ASCT followed by RIT, and 2 of the trials with long-term follow-up showed improved OS, the rates of extensive chronic GVHD remain high, and data are marred by the genetic randomization and the small numbers of patients with inconsistently defined high-risk disease. Table 2 summarizes the results from clinical trials comparing tandem ASCT versus ASCT followed by RIT.

RIT has also been evaluated in relapsed MM. Although most of the clinical data are from smaller case series, some patients have clearly enjoyed prolonged remissions with this approach.\textsuperscript{56,57} One retrospective trial evaluated patients who underwent HLA typing within 30 days after relapse from ASCT and compared those who received RIT within 1 year of relapse versus those who did not. Findings showed that PFS was significantly prolonged in those who received RIT (2-year PFS, 42% vs 18%; \(P < .001\)) but OS was unchanged (2-year OS, 54% vs 53%; \(P = .329\)), and there was a cumulative nonrelapse mortality rate of 22%.\textsuperscript{58} These data are similar to results from a retrospective study conducted by the EBMT evaluating 413 patients who underwent an ASCT. The median OS and PFS were 24.7 and 9.6 months, respectively, and 26.7% of evaluable patients had extensive chronic GVHD; the nonrelapse mortality rate was 21.5% at 1 year and 28.4% at 3 years, with donor and recipient cytomegalovirus seropositivity linked to worse outcomes.\textsuperscript{59}

**Conclusions**

Although much has been accomplished in the treatment of MM, the disease remains incurable, and patients with the highest-risk disease have a very poor prognosis. The benefit of additional cytoreduction afforded by either single or tandem ASCT is largely based on older clinical data and needs to be redefined in light of advances in induction and consolidation/maintenance therapies. Improved high-dose regimens inclusive of novel agents and the innovative use of radiation therapies may also be needed.\textsuperscript{60,61} The role of allo-SCT and RIT in MM is still uncertain. Until mature data become available from randomized trials comparing outcomes with or without ASCT following modern-day induction therapy, ASCT should remain part of the treatment strategy for transplant-eligible patients with MM.

**References**


