Introduction

Multiple myeloma is a clonal plasma cell neoplasm with sensitivity to a broad array of antineoplastic agents including alkylating agents, anthracyclines, corticosteroids, radiation therapy, immunomodulators, and proteasome inhibitors. It accounts for approximately 10% of all hematologic malignancies. Novel antimyeloma agents such as bortezomib and lenalidomide used in combination with conventional drugs, including dexamethasone, have demonstrated significantly higher response rates, in both front-line and relapsed settings. Although multiple therapeutic agents have been introduced into clinical

Background: Multiple myeloma is largely an incurable malignant plasma cell neoplasm; however, the landscape of its treatment is rapidly changing.

Methods: The recent literature on both autologous and allogeneic transplant approaches for multiple myeloma was reviewed.

Results: High-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) remains an integral component of upfront treatment strategy, and the incorporation of novel immunomodulators and proteasome inhibitor to induction regimens improves response rates and increases overall survivals. Bortezomib- and lenalidomide-based combination chemotherapy regimens have become the standard induction myeloma therapy. When myeloma patients proceed to transplant after novel combination regimens, their response rates are further improved. Despite these recent major improvements, myeloma remains incurable and long-term survival appears elusive. Due in part to a potential graft-vs-myeloma effect, allogeneic HCT is a potentially curative transplant option. However, initial attempts have been hampered by the high transplant-related mortality. With a reduction of toxicity, allogeneic transplant approaches with reduced-intensity conditioning have been utilized, although they are subject to continued disease progression and relapse following transplantation. Recent research efforts have shifted to the use of a tandem autologous-allogeneic HCT approach. The long-term follow-up of this new strategy is awaited.

Conclusions: Recent advances in HCT have improved outcomes of patients with multiple myeloma. Ongoing research activity focuses on the strategies to improve outcomes of HCT by incorporation of tandem autologous-allogeneic transplantation schema, novel conditioning regimens, and the use of consolidation and maintenance therapy.
practice recently, multiple myeloma remains virtually incurable. Based on the successful control of refractory malignant hematologic disorders with hematopoietic cell transplantation (HCT), application of HCT in multiple myeloma has been explored extensively using both autologous and syngeneic grafts. Either autologous or syngeneic HCT allows the intensive conditioning regimen with high-dose chemotherapy and/or radiation to eradicate residual myeloma, as the infusion of hematopoietic progenitor cells would overcome marrow aplasia secondary to high-dose therapy and thus facilitate hematologic recovery. There would be the added immunologic advantage of graft-vs-myeloma effect when HCT from a suitable allogeneic donor is performed.

**Autologous HCT for Multiple Myeloma**

Prospective randomized trials comparing conventional chemotherapy with high-dose therapy followed by autologous HCT (autoHCT) for patients with multiple myeloma have been conducted extensively. An Intergroupe Francophone du Myélome (IFM) study demonstrated that high-dose melphalan and total body irradiation (TBI) followed by autoHCT, when used as consolidation after induction therapy with conventional chemotherapy, could result in higher response rates, longer disease-free survivals, and improved overall survival (OS) compared with continuation of conventional chemotherapy. Child et al reported the results of the Medical Research Council Myeloma VII trial in which combination chemotherapy was compared with combination chemotherapy followed by high-dose melphalan and autoHCT. With 407 patients enrolled, the autoHCT arm showed a 12-month improvement in both the median OS (P = .04) and event-free survival (EFS). A meta-analysis of 9 randomized controlled trials for autoHCT comprising 2,411 patients showed the combined hazard of death of 0.92 (95% confidence interval [CI], 0.74-1.13) and the combined hazard of progression of 0.75 (95% CI, 0.59-0.96), indicating progression-free survival (PFS) benefit but no definitive OS benefit with autoHCT. Based on these studies, high-dose chemotherapy followed by autoHCT has become an integral upfront treatment modality for multiple myeloma and remains the leading indication for autoHCT in North America.

**Continuous Risk of Relapse After Autologous Transplantation**

Despite the favorable therapeutic impact of high-dose therapy followed by autoHCT, disease relapse after autologous transplant remains a continuous risk, and the majority of patients succumb to recurrent disease. Disease recurrence is presumably secondary to (1) persistent disease in the bone marrow after transplant due to drug resistance and/or (2) the reinfusion of contaminating malignant plasma cells in the stem cell graft. This view is supported by the lower relapse rates seen after syngeneic transplantation compared to autoHCT. Purging strategies to reduce the contaminating myeloma cells have been evaluated. However, even with a 3 to 4 logs reduction of myeloma cells in the graft, randomized studies showed no improvement in responses, PFS, or OS. The reasons for the disappointing result may be that only a minute fraction of tumor cells may be required in the graft for relapse or residual myeloma cells in the marrow after transplant may be responsible for the ultimate disease relapse.

In an effort to reduce minimal residual disease after autoHCT, additional therapies have been delivered either with a second autoHCT in a tandem fashion or with a reduced-intensity conditioning (RIC) followed by allogeneic HCT (alloHCT). When compared with single autoHCT, some randomized studies of tandem autoHCT have shown approximately a 10% improvement in OS. The survival benefit was mainly seen in patients who achieved less than very good partial response (VGPR) after first transplant. Caution should be exercised as the finding was noted in an unplanned subgroup analysis and the studies predated the currently available novel antimyeloma agents. This also suggests that even patients who achieved complete response (CR) after autoHCT still harbor highly resistant myeloma cells in the marrow. Additionally, some studies have demonstrated the influence of disease biology on outcomes of autoHCT. Cytogenetic abnormalities detected in the myeloma cells by fluorescence in situ hybridization (FISH), including deletion of chromosome 13, translocation of chromosomes 4 and 14, and deletion of chromosome 17, have been associated with significantly shorter PFS and OS than those patients without these abnormalities. It has also been shown that deletion 13 detected only by FISH or as a sole abnormality without t(4;14) or 17p deletion does not carry the same prognostic significance.

**Induction Regimens Prior to Autologous Transplantation**

With the goal of improving overall responses following autoHCT, the search for more efficacious induction regimens continues to improve outcomes of transplant for patients with multiple myeloma. In certain cases, the novel agents may overcome high-risk disease biology. A variety of combinations have incorporated novel agents into induction regimens for patients with newly diagnosed multiple myeloma. Table 1 summarizes selected trials that reported comparisons of combinations incorporating novel agents with traditional regimens such as vincristine, doxorubicin, and dexamethasone (VAD) given prior to autoHCT. The Hovon group incorporated thalidomide as an induction therapy (TAD regimen: thalidomide, doxorubicin, and dexamethasone) and demonstrated improved remission status following induction over the VAD control group and superior response after autoHCT. Barlogie et al implemented a more intensified strategy...
and added thalidomide to induction therapy and between tandem transplants, consolidation, and maintenance regimens in their Total Therapy approach at the University of Arkansas. The addition of thalidomide showed increased CR rates and prolonged EFS, although OS remained the same and more adverse events were noted in the thalidomide group. The IFM 2005-01 study compared induction therapy with bortezomib plus dexamethasone with VAD in patients undergoing autoHCT in an open-label phase III randomized trial.25 The trial enrolled 482 patients and the results showed substantially greater VGPR and CR rates after bortezomib plus dexamethasone induction compared with VAD. Following autoHCT, further improvement in responses with bortezomib plus dexamethasone induction was achieved. There was a trend toward better PFS (36.0 months vs 29.7 months; P = .064) with bortezomib plus dexamethasone. However, there was no difference in 3-year OS rates (81.4% vs 77.4%) with a median follow-up of 32.2 months. The Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) compared the combination of bortezomib, thalidomide, and dexamethasone (VTD) with thalidomide plus dexamethasone (TD).29 A total of 480 patients were enrolled and received induction regimens, tandem transplants, followed by consolidation and maintenance regimens. The VTD regimen was shown to be substantially more effective than the TD regimen in producing major responses after induction therapy. There was a further improvement in major responses following transplants, with significant advantages with VTD combination.

The Eastern Cooperative Oncology Group (ECOG) conducted a comparison study of lenalidomide plus either high-dose dexamethasone (40 mg on days 1–4, 9–12, and 17–20) vs low-dose dexamethasone (40 mg on days 1, 8, 15, and 22).28 A total of 445 patients were randomly assigned to the study regimens. After the induction therapy, 167 patients interrupted or stopped treatment to have stem cell harvest. The high-dose dexamethasone group had higher responses; however, at the interim analysis at 1 year, OS was higher in the low-dose dexamethasone group (presumably secondary to toxic effects from high-dose dexamethasone). This led to trial stoppage, and the patients on the high-dose dexamethasone arm were crossed over to low-dose therapy. In aggregates, certain novel induction regimens may result in a higher frequency of major responses than the traditional regimens, and high-dose therapy followed by autoHCT further improves major response rates. In a single-arm study, the Italian group conducted a prospective trial utilizing an induction regimen of bortezomib, doxorubicin, and dexamethasone (PAD) followed by tandem autoHCT with melphalan 100 mg/m² in newly diagnosed myeloma patients who were between 65 and 70 years of age.31 Patients also received consolidation with lenalidomide plus prednisone followed by lenalidomide maintenance. A total of 102 patients were enrolled. After PAD induction, 58% achieved VGPR or better with a CR rate of 13%. Following melphalan and autoHCT, 82% had at least VGPR, and the CR rate increased to 38%. After a median follow-up of 21 months, the 2-year OS rate was 86%, again underscoring the promising use of novel agents in the induction and improved outcomes following autoHCT. It is important to note that no convincing data currently exist based on phase III studies to suggest that long-term treatment with novel drug regimens would translate into either equivalent or superior survival with autoHCT.

### Novel Conditioning Regimens for Autologous Transplantation

Bortezomib has been shown to have a significant clini-

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**Table 1. — Selected Phase III Studies of Novel Induction Regimens Prior to Autologous HCT**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Post-Induction (%)</th>
<th>Post-AutoHCT(s) (%)</th>
<th>Overall Survival (%)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>≥ nCR</td>
<td>≥ VGPR</td>
<td>≥ nCR</td>
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<tr>
<td>Harousseau et al²⁵</td>
<td>240</td>
<td>bortezomib + dexamethasone VAD</td>
<td>14.8</td>
<td>37.7</td>
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<td></td>
<td>242</td>
<td>VAD</td>
<td>8</td>
<td>15.1</td>
<td>18.4</td>
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<tr>
<td>Cavo et al²⁶</td>
<td>236</td>
<td>VTD</td>
<td>311</td>
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<tr>
<td></td>
<td>238</td>
<td>TD</td>
<td>1</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>Lokhorst et al²⁷</td>
<td>201</td>
<td>TAD</td>
<td>3</td>
<td>33</td>
<td>16</td>
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<tr>
<td></td>
<td>201</td>
<td>VAD</td>
<td>2</td>
<td>15</td>
<td>11</td>
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<tr>
<td>Rajkumar et al²⁸</td>
<td>214</td>
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<td>18</td>
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</tr>
<tr>
<td></td>
<td>208</td>
<td>Rd</td>
<td>14</td>
<td>40</td>
<td>NR</td>
</tr>
</tbody>
</table>

HCT = hematopoietic cell transplantation, nCR = near complete response, VGPR = very good partial response, VAD = vincristine, doxorubicin, and dexamethasone, VTD = bortezomib, thalidomide, and dexamethasone, TD = thalidomide plus dexamethasone, TAD = thalidomide, doxorubicin, and dexamethasone, RD = lenalidomide plus high-dose dexamethasone, Rd = lenalidomide plus low-dose dexamethasone, NR = not reported.
cal antmyeloma effect in combination with melphalan.32–35 Bortezomib targets both acquired and de novo mechanisms of drug resistance and sensitizes melphalan-sensitive and -resistant myeloma cell lines to melphalan via inhibition of nuclear factor kappa B (NF-κB) with reduction in DNA damage repair and enhanced melphalan sensitivity.34–36 It has been proposed that bortezomib in combination with high-dose melphalan may be synergistic and may provide significant clinical benefit.37 Other investigators have combined bortezomib with high-dose melphalan. In a multicenter phase III, Roussel et al38 reported at least a 70% VGPR rate, including a CR rate of 32%, after autoHCT in newly diagnosed multiple myeloma patients with melphalan plus bortezomib conditioning. Bortezomib was given intravenously at 1 mg/m² on days -6, -3, +1, and +4. A group at Emory University performed a dose-and-schedule-finding randomized phase I/II study by administering bortezomib either before or after high-dose melphalan in myeloma patients.39 Pharmacodynamic studies showed greater plasma cell apoptosis among patients who received bortezomib following melphalan,39 suggesting the importance of administration sequence for the synergism enhancement.34 Our group has recently completed a phase I/II study of bortezomib plus high-dose melphalan and tandem autologous transplantation in patients with primary resistant myeloma.37,40 The maximum planned dose of bortezomib at 1.3 mg/m² was successfully combined with high-dose melphalan and was well tolerated. The peak of a best overall response rate of 84% was achieved after tandem transplants, and the CR rate was 36%. The median OS in this poor-risk group was 35 months. This is an active area of research, and results of prospective randomized trials to confirm these positive findings are awaited.

**Consolidation and Maintenance After Autologous Transplantation**

The traditional approach before the availability of novel agents was to consolidate a response achieved with a first autoHCT by performing a second autoHCT procedure in a tandem fashion, and the use of a second autoHCT was usually reserved for patients not achieving at least a VGPR to the first transplant.30 Efforts have been made to utilize novel agents soon after autoHCT to further improve the depth and quality of responses. The Italian group has treated 39 patients who achieved at least a VGPR after autoHCT with 4 courses of bortezomib, thalidomide, and dexamethasone (VTD).41 Immunofixation CR rates increased from 15% after autoHCT to 49% after VTD consolidation following autoHCT. Molecular remissions were observed in 3% of patients after autoHCT and in 18% after VTD consolidation. In a larger randomized phase III trial, the Nordic Myeloma Group evaluated a role of single-agent bortezomib as consolidation after autoHCT.42 The response following HCT was improved, and the 6-month CR or near CR rate was 35% in the observation arm vs 54% in the bortezomib arm (P < .005). No data are yet available regarding survival. The impact of novel agent-containing consolidation regimens after autoHCT has been investigated in ongoing trials, one of which is currently being performed by the Blood and Marrow Transplant Clinical Trials Network. This trial (BMT CTN 0702) is comparing 4 cycles of a triplet combination of lenalidomide, bortezomib, and dexamethasone with either no consolidation or a second autoHCT.

Maintenance/consolidation chemotherapy after autoHCT has been actively investigated as another modality to improve responses, EFS, and OS.43 Thalidomide maintenance has been shown to improve OS in at least 2 of 4 phase III trials. However, thalidomide is not widely used in clinical practice, presumably reflecting concerns regarding cumulative toxicity.29,44–45 An Arkansas study reported that the incidence of grade 3 to 4 peripheral neuropathy was 27% where treatment occurred over a prolonged period.29 Lenalidomide is not considered neurotoxic, and the results of the two randomized trials evaluating the use of lenalidomide as maintenance therapy have been presented. In the IFM 2005-02 study, 614 patients were randomized to receive consolidation with lenalidomide (25 mg/day, 21 days out of 28-day schedule for 2 months) followed by maintenance with either placebo or lenalidomide (10 to 15 mg/day until disease relapse) after autoHCT.46 After the first preplanned interim analysis showed PFS superiority in the lenalidomide arm, the data and safety monitoring committee recommended unblinding the trial. After a median follow-up of 24 months from the randomization, the final result showed that maintenance with lenalidomide improved PFS (42 months vs 24 months from randomization; P < 10–6). This benefit was observed across all stratified subgroups. The maintenance was well tolerated, and the rate of definitive interruption due to serious adverse events was similar in both arms.

The Cancer and Leukemia Group B also reported a similar phase III randomized trial of lenalidomide after autoHCT (CALGB 100104 study).47 A total of 460 patients were randomly assigned to receive either placebo or lenalidomide 10 mg per day until disease progression. The study was stopped due to the superiority of the lenalidomide arm, with a 61% reduction in risk of disease progression. The preliminary estimated median time to progression was 42.3 months for the lenalidomide arm and 21.8 months for the placebo arm. The toxicity profiles were analogous to those described in the IFM 2005-02 study, again confirming the feasibility of this maintenance approach. Taken together, the two separate randomized phase III trials have shown the remarkable impact of lenalidomide on disease control following autoHCT, although the results are preliminary. A long-term follow-up is required to fully assess the survival benefit of lenalidomide maintenance.

Recently, increased instances of second primary malignancies, including both hematologic malignancies
and solid tumors, have been observed in patients who received lenalidomide compared to those receiving the control. In both the CALGB 100104 study and the IFM 2005-02 study, the rates of second primary malignancies appeared to be in the range of 5%. However, this observation requires careful interpretation since lenalidomide prolongs PFS, and the experimental arms may be subject to more rigorous reporting while they are on the study; this may introduce a reporting bias. These data are preliminary, and further follow-up with cautious examination of the risk of second primary malignancies in lenalidomide maintenance is warranted prior to drawing definitive conclusions.

**Allogeneic HCT**

AlloHCT from HLA-antigen matched related or unrelated donors is a treatment modality with curative potential for myeloma patients. HCT from autologous or syngeneic donors provides little or no immunologic effect against myeloma cells. Long-term follow-up of recipients of autoHCT indicates a continuous risk of disease recurrence for many years following transplant, and patients are rarely cured. In contrast, studies of alloHCT with long-term follow-up appear to show durable remissions and a lower risk of recurrence. Advantages of an alloHCT include the use of a tumor-free graft and the immune-mediated graft-vs-myeloma effect.

Although high-intensity conditioning followed by alloHCT results in long-term durable remissions and has a curative potential, transplant-related mortality (TRM) is the major challenge and thus not all patients are candidates for this treatment approach. AlloHCT with myeloablative conditioning has been traditionally offered to younger patients with good performance status or to those who were refractory to conventional chemotherapy primarily due to the high TRM and morbidity associated with the intense myeloablative conditioning regimen. Since the turn of the century, indications for an alloHCT have been dramatically expanded following the introduction of reduced-intensity or nonmyeloablative conditioning regimens designed more for immunosuppression than for cytoreduction, with the aim of establishing consistent donor engraftment while minimizing toxicity and damage to normal host tissues. These regimens broadened the applicability of alloHCT to patients up to 70 years of age, even in those with multiple pre-existing comorbid conditions. In these newer strategies, autoHCT was sequenced with alloHCT to first debulk myeloma and then to subsequently eradicate tumor by alloreactive donor T cells.

**Reduced-Intensity Conditioning Regimens**

Based on the observed benefit of graft-vs-myeloma in disease control, investigators have further explored highly immunosuppressive but less toxic conditioning regimens that could safely facilitate engraftment while reducing TRM. These conditionings were termed reduced-intensity and nonmyeloablative regimens depending on the intensity of the dose or combination of agents. The most widely used RIC regimen was originally developed in Seattle where preclinical canine transplant studies demonstrated stable donor cell engraftment after a truly nonmyeloablative regimen consisted of low-dose TBI (2 Gy) and a combination of two potent immunosuppressive agents including cyclosporine and mycophenolate mofetil. This platform was soon translated to clinical application, with 18 patients undergoing alloHCT for multiple myeloma. Of those patients, 7 had refractory myeloma and 6 had failed prior autoHCT. Two of the first 4 patients rejected the donor graft, which led to the addition of fludarabine to provide additional immunosuppression and stable engraftment. Of the 18 patients, 1 died due to transplant-related toxicities, CR occurred in 2 patients, and 3 additional patients achieved PR. None of the responses were durable. This observation suggests that the graft-vs-myeloma effect is relatively modest and the additional cytoreduction would be necessary to improve the outcome of RIC allografting.

Several studies of RIC allografts from either matched or unmatched donors have shown that the results are generally poor, especially when patients have refractory disease or have failed prior autoHCT; the 2-year survival rates range from 26% to 50%. A study combining data from 120 patients with multiple myeloma transplanted with fludarabine plus melphalan conditioning from multiple international centers showed that relapse from a prior autoHCT was the most significant prognostic risk factor for TRM (hazard ratio [HR] = 2.80; P = .02), relapse (HR = 4.14; P < .001), and death (HR = 2.69; P = .005). The European Group for Blood and Marrow Transplantation (EBMT) reported its large retrospective registry data comparing myeloablative and nonmyeloablative conditioning. TRM was significantly reduced with RIC regimens; however, OS was equivalent due to higher relapse and progression with RIC allografting. The study was also limited due to significant differences in prognostic variables and treatment modalities used between the two groups. At least one trial comparing second autoHCT with RIC allografting following relapse from a prior autoHCT found no significant differences in PFS and OS. Subsequently, another study has demonstrated that a second autoHCT may result in major responses with prolonged survival. Hence, the choices of transplant option after failed autoHCT remain subject to further research.

**Tandem Autologous Reduced-Intensity Allogeneic Transplantation Approach**

With an effort to improve cytoreduction, a novel treatment modality was designed for patients with newly diagnosed multiple myeloma where an initial autoHCT is followed by a low-dose TBI-based nonmyeloablative al-
lograft approximately 2 to 4 months later. The rationale for the tandem auto-alloHCT approach was to separate in time (1) cytoreduction with standard high-dose melphalan at 200 mg/m² and (2) the graft-vs-myeloma effect with the potential for dramatically reducing the TRM. The initial multicenter prospective trial by the Seattle Consortium enrolled 54 newly diagnosed patients with stage II–III myeloma. The median age was 52 years, and half of the patients had refractory or relapsed disease. All patients achieved full donor chimerism except 1 patient who required donor lymphocyte infusion due to partial chimerism. The CR and TRM rates were 57% and 22%, respectively. After a median follow-up of 60 months, the OS rate was 69% and the PFS rate was 38%. The long-term outcomes using the same approach after 6.3 years of follow-up was reported, even though the tandem auto-alloHCT was not used in the first-line setting in all patients. Grade II–IV acute graft-vs-host disease (GVHD) occurred in 42% of patients, and 74% experienced chronic GVHD. The TRM rate at 5 years was 18%, primarily due to GVHD and/or infections. The overall response rate was 94% (CR = 65%, PR = 29%). Median OS was not reached, and PFS was 3 years (Table 2).

A prospective multicenter study by the Gruppo Italiano Trapianti di Midollo Osseo (GITMO) enrolled 100 newly diagnosed multiple myeloma patients who were < 65 years of age. With a median follow-up of 5 years, OS was not reached and EFS was 37 months (Table 2). Acute and chronic GVHD occurred in 38% and 50% of patients, respectively. CR was achieved in 53% of patients. Achievement of CR or VGPR prior to allografting was associated significantly with achievement of posttransplant remission and longer EFS. Table 2 summarizes several phase II trials of tandem auto-alloHCT in patients with both newly diagnosed and relapsed multiple myeloma following autoHCT. Several other reduced-intensity regimens have been reported, including melphalan 100 mg/m² to 140 mg/m² with or without fludarabine, 2 Gy TBI with or without fludarabine, and intermediate-dose busulfan. Antithymocyte globulin (ATG) or alemtuzumab has also been utilized for in vivo T-cell depletion to reduce the incidence of GVHD.

Comparison of Tandem Autologous and Tandem Auto-AlloHCT Approaches

Recent trials comparing the platform of tandem auto-alloHCT with a tandem autologous approach are summarized in Table 3. The IFM study treated 284 newly diagnosed myeloma patients with high-risk features (elevated β2-microglobulin and chromosome 13 deletion) on two protocols: IFM99-03 and IFM99-04. All patients received VAD induction followed by first autoHCT with

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Donor</th>
<th>Regimen</th>
<th>GVHD Prophylaxis</th>
<th>%</th>
<th>Overall Survival</th>
</tr>
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<tbody>
<tr>
<td>Rotta et al</td>
<td>102</td>
<td>MRD</td>
<td>Autologous</td>
<td>Mel 200 (n = 2)</td>
<td>TBI 2 Gy + Flu 30 mg/m² (n = 27)</td>
<td>CSA + MMF</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Allogeneic</td>
<td>Mel 140 (n = 1)</td>
<td>TBI 2 Gy</td>
<td>CSA + MMF</td>
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<tr>
<td>Bruno et al</td>
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<tr>
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<td>TBI 2 Gy</td>
<td>Flu 30 mg/m²</td>
<td>CSA + MMF</td>
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<tr>
<td>Lee et al</td>
<td>45</td>
<td>MUD</td>
<td>Autologous</td>
<td>Not specified</td>
<td>Mel 100 (MUD) + TBI 1.2 Gy + Flu 60 mg/m²</td>
<td>CSA (MUD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allogeneic</td>
<td>Mel 100 + TBI 1.25 Gy + Flu 60 mg/m²</td>
<td>CSA + MP (MUD)</td>
<td>36 at 2 yrs</td>
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<td>36 at 2 yrs</td>
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<td>Kröger et al</td>
<td>49</td>
<td>MUD</td>
<td>Autologous</td>
<td>Not specified</td>
<td>Flu 90 mg/m² + Mel 140</td>
<td>ATG 20 mg/kg x 3 doses</td>
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<td>Allogeneic</td>
<td>Not specified</td>
<td>Mel 140</td>
<td>Flu 150 mg/m² + Cy 2 mg/m²</td>
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GVHD = graft-vs-host disease, aGVHD = acute GVHD, cGVHD = chronic GVHD, TRM = transplant-related mortality, MRD = matched related donor, MUD = matched unrelated donor, Mel 200 = melphalan at 200 mg/m², Mel 140 = melphalan at 140 mg/m², Mel 100 = melphalan at 100 mg/m², BEAM = etoposide, rabinobside, acytarabine, melphalan, TBI = total body irradiation, Flu = fludarabine, CSA = cyclosporine, MMF = mycophenolate mofetil, TAG = tacrolimus, ATG = antithymocyte globulin, MP = methylprednisolone.

* Grade III–IV acute GVHD.
high-dose melphalan at 200 mg/m². Sixty-five patients with matched related donors subsequently received an allograft with busulfan, fludarabine, and high-dose ATG 12.5 mg/kg conditioning (IFM99-03). This arm was compared with 219 patients who underwent a second autoHCT after high-dose melphalan at 220 mg/m² (IFM99-04), given the proven benefit of tandem autoHCT by the IFM³⁸ and suboptimal disease control with single autoHCT in high-risk patients.²⁵ TRM and response rates were similar. At a median follow-up of 2 years, the OS and EFS rates were 35% and 25%, respectively, in the tandem auto-alloHCT cohort and 41% and 30% in the tandem autoHCT cohort (Table 3). These findings suggest that patients with high-risk features did not benefit from an RIC alloHCT. It is possible that the administration of high-dose ATG might have hindered, to some extent, the potentially curative graft-vs-myeloma effects as the incidence of chronic GVHD was only 7%. The impact of myeloma biology based on genetic abnormalities with regard to alloHCT outcomes warrants further study.

The Italian group enrolled 162 consecutive younger patients ≤ 65 years of age with newly diagnosed myeloma who had at least one sibling.⁷⁸ Elevated β2-microglobulin level (≥ 3.5 mg/L) and chromosome 13 deletions were seen in 35% (n = 143) and 40% (n = 52) of patients, respectively. All patients received a VAD-based induction regimen followed by autoHCT with melphalan conditioning. Eighty patients with matched related donors were offered a TBI-based nonmyeloablative regimen followed by autoHCT with melphalan conditioning. Twenty-two patients with either second autoHCT (n = 85) or RIC with fludarabine and melphalan followed by allografting (n = 25), depending on the availability of a matched related donor. CR rates were 55% vs 26% and TRM rates were 10% and 2%, respectively. Median OS was not reached in the tandem auto-alloHCT cohort and was 58 months in the tandem autologous arm. EFS was 43 months in the tandem auto-alloHCT arm and 33 months in the tandem autoHCT arm, respectively.⁷⁹ In a multivariate analysis classifying patients based on either high β2-microglobulin or chromosome 13 abnormality (ie, high-risk group), the adjusted HRs were 0.34 (95% CI, 0.10–1.18) for OS and 0.52 (95% CI, 0.22–1.21) for EFS. These results were similar to those noted for all 162 patients combined.

Another biologic randomization study has been reported by the Spanish PETHEMA group.⁸¹ A total of 110 patients with newly diagnosed myeloma who failed to achieve at least near CR after a first autoHCT were treated with either second autoHCT (n = 85) or RIC with fludarabine and melphalan followed by allografting (n = 25), depending on the availability of a matched related donor. The CR rate was higher in the tandem auto-alloHCT arm (40% vs 11%; P = .001). There was a trend toward

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>GVHD Prophylaxis</th>
<th>aGVHD II–IV</th>
<th>cGVHD</th>
<th>TRM</th>
<th>Complete Remission</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno et al⁷⁸</td>
<td>80</td>
<td>Mel 200 → Mel 200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>26</td>
<td>53 at 4 yrs</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>Mel 200 → TBI 2 Gy</td>
<td>NA + CSA + MMF</td>
<td>43</td>
<td>32</td>
<td>10</td>
<td>55</td>
<td>75 at 4 yrs</td>
</tr>
<tr>
<td>Garban/Moreau⁷⁹,⁸⁰</td>
<td>219</td>
<td>Mel 200 → Mel 220</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>33</td>
<td>44 at 5 yrs</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Mel 200 → Bu Flu ATG</td>
<td>NA + CSA + MTX</td>
<td>24</td>
<td>43</td>
<td>11</td>
<td>33</td>
<td>33 at 5 yrs</td>
</tr>
<tr>
<td>Rosiñol et al⁸¹</td>
<td>85</td>
<td>Mel 200 → Mel 200 or CVB</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>11</td>
<td>60 at 5 yrs</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Mel 200 → Flu Mel 140</td>
<td>NA + CSA + MTX</td>
<td>32</td>
<td>66</td>
<td>16</td>
<td>33</td>
<td>62 at 5 yrs</td>
</tr>
<tr>
<td>Knop et al⁸²</td>
<td>73</td>
<td>Mel 200 → Mel 200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>16</td>
<td>32</td>
<td>70 at 3 yrs</td>
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<tr>
<td></td>
<td>126</td>
<td>Mel 200 → Flu Mel 140 + ATG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>16</td>
<td>59</td>
<td>60 at 3 yrs</td>
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<tr>
<td>Lokhorst et al⁸³</td>
<td>141</td>
<td>Mel 200 → maintenance</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>14</td>
<td>42</td>
<td>56 at 4 yrs</td>
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<tr>
<td></td>
<td>126</td>
<td>Mel 200 → TBI 2 Gy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>14</td>
<td>45</td>
<td>63 at 4 yrs</td>
</tr>
<tr>
<td>Gahrton et al⁸⁴</td>
<td>251</td>
<td>Mel 200 → Mel 200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
<td>38</td>
<td>57 at 5 yrs</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>Mel 200 → Flu TBI 2 Gy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
<td>43</td>
<td>60 at 5 yrs</td>
</tr>
</tbody>
</table>

GVHD = graft-vs-host disease, aGVHD = acute GVHD, cGVHD = chronic GVHD, TRM = transplant-related mortality, Mel 200 = melphalan at 200 mg/m², Mel 220 = melphalan at 220 mg/m², Mel 140 = melphalan at 140 mg/m², TBI = total body irradiation, CSA = cyclosporine, MMF = mycophenolate mofetil, Bu = busulfan, Flu = fludarabine, CVB = cyclophosphamide, etoposide, BCNU, ATG = antithymocyte globulin, MTX = methotrexate, TBI = total body irradiation, NA = not applicable, NR = not reported.
a longer PFS (median = 31 months vs not reached; \( P = .08 \)) in the RIC group, which is in line with the result reported by the Italian group showing lower relapse rates after tandem auto-alloHCT than after tandem autoHCT. However, TRM appeared to be higher in the tandem auto-alloHCT patients (16% vs 5%; \( P = .07 \)). There were no statistically significant differences in OS and EFS (Table 3), which may be due in part to the smaller number of patients treated in the tandem auto-alloHCT arm.

In 2010, the BMT CTN reported a multicenter phase III trial (BMT CTN 0102) in which patients were biologically assigned based on availability of a matched related donor to either tandem autoHCT using melphalan 200 mg/m² or tandem auto-alloHCT using melphalan 200 mg/m² followed by alloHCT with 2 Gy TBI.\(^{85,86}\) GVHD prophylaxis consisted of cyclosporine and mycophenolate mofetil. The primary endpoint of the study was 3-year PFS in patients with standard-risk disease (absence of chromosome 13 deletion by metaphase karyotype and \( \beta 2 \)-microglobulin < 4 mg/L). Among the 710 patients enrolled between 2003 and 2007 at 37 US centers, 625 patients had standard risk. Patients assigned to tandem autoHCT arm were further randomized to maintenance with thalidomide plus dexamethasone for 1 year post-transplant or observation. Compliance with maintenance was low, and PFS and OS were not different between maintenance and observation. Hence, these two tandem autoHCT arms were combined for the comparison with the tandem auto-alloHCT arm. Patients in the tandem autoHCT arm (\( n = 189 \)) were older, with a median age of 55 years vs 52 years (\( P = .01 \)). The 3-year PFS rates were 46% and 43% (\( P = .67 \)), the 3-year OS rates were 80% and 77% (\( P = .19 \)) for the tandem autoHCT and the tandem auto-alloHCT groups, and the 3-year TRM rates were 4% and 11% (\( P = .04 \)), respectively. Among the tandem auto-alloHCT patients, probabilities of grade III-IV acute and chronic GVHD were 9% and 47%, respectively. Eighty-two percent of patients in each arm received the assigned second transplant. At 3 years, the study did not show added benefit of the auto-alloHCT approach over tandem autoHCT.\(^{85,86}\) Other studies in myeloma demonstrated that differences in survival may appear beyond 5 years from the time of transplant, thus further follow-up will be important to assess the true benefit of the tandem auto-alloHCT approach over tandem autoHCT.\(^{84}\)

**Conclusions**

Major progress has been made in the treatment of multiple myeloma in recent years, including the introduction of novel agents and transplant strategies. Many studies stress the importance of achieving a deeper response, ie, VGPR or better, as a surrogate for improved survival. However, even with significant advances in the field, multiple myeloma remains incurable for the majority of patients. Ongoing research efforts have focused on the integration of novel agents to induction regimen to improve initial response followed by high-dose therapy and autoHCT and consideration of incorporating reduced-intensity alloHCT in tandem fashion under clinical trials to achieve better long-term disease control. The availability of several newer agents in the pipeline and incorporation of these agents into the induction regimen may further improve OS for myeloma patients who are candidates for both autoHCT and alloHCT in the future. Further research is required to develop novel strategies in order to achieve a cure for patients with multiple myeloma.

**References**


