



**TABLE OF CONTENTS**

**Introduction**

**Induction Therapy**

**Conditioning  
Regimens**

**Stem Cell  
Transplantation**

**Therapeutic  
Strategies**

**Conclusion**

**References**

## **Novel Drug Combinations and Stem Cell Transplantation in Multiple Myeloma**

November 17, 2009

William Bensinger, MD

### **Introduction**

---

The use of high-dose chemotherapy and autologous stem cell transplantation has become standard therapy for patients with multiple myeloma (MM), leading to improvements in both response rates and survival outcomes. Not all patients meet the eligibility criteria for transplantation, however, and the myriad options for induction therapy and transplantation itself present a daunting range of risks and benefits to be evaluated when selecting the proper course of therapy for individual patients.

In this monograph, William Bensinger, MD, Professor of Medicine at the University of Washington, Director of the Autologous Transplant Program at the Fred Hutchinson Cancer Research Center in Seattle, and a member of the National Comprehensive Cancer Network Multiple Myeloma Panel, discusses the relevance of stem cell transplantation in the context of novel drug combinations and emerging clinical trial data concerning the optimal management of MM. In addition to stem cell transplants, the approval of 2 new classes of drugs, immunomodulators and proteasome inhibitors, has revolutionized care among patients with MM, and compelling data continue to emerge. Dr. Bensinger draws upon his vast clinical experience to offer his expert commentary on the latest findings in this continually evolving therapeutic area.

---

### **Primary Induction Therapy for Transplantation Candidates**

---

The initial treatment of multiple myeloma depends on a patient's eligibility for stem cell transplantation. During the last decade, higher rates of complete response (CR) and prolonged duration of progression-free survival (PFS) and overall survival (OS) have been achieved using high-dose chemotherapy plus autologous

stem cell transplantation (HDT-ASCT). Depth of response, ie, achievement of CR or very good partial response (VGPR), is a key prognostic factor for prolonged survival,<sup>1</sup> and eradication of minimal residual disease is crucial to long-term results.<sup>2</sup>

**Novel Drug Combinations: Two vs Three Drugs.** Dose intensification using HDT-ASCT results in improved response rates and improved survival over outcomes achieved with conventional therapy. HDT-ASCT is the standard approach for patients with multiple myeloma who are able to tolerate the procedure. For these transplantation candidates, newer induction regimens using novel agents have replaced the older regimen of vincristine, doxorubicin, and dexamethasone (VAD). The most common induction regimens currently in use are those involving thalidomide (thalidomide plus dexamethasone [TD]), bortezomib (eg, bortezomib, thalidomide, and dexamethasone [VTD]; bortezomib, doxorubicin, and dexamethasone [PAD]), and lenalidomide (lenalidomide plus dexamethasone [RD]).

**RD vs D.** Induction therapy with RD resulted in an 18% CR rate and a 91% overall response rate (ORR).<sup>3</sup> The main toxicities were hematologic effects (>50% of patients), fatigue, and muscle weakness (<10%). The 2-year PFS and OS were 83% and 92%, respectively, among patients who stopped induction and continued on to SCT. The Eastern Cooperative Oncology Group (ECOG) study E4A03 reported higher rates of CR, near CR (nCR), and VGPR using lenalidomide and a higher dose of dexamethasone.<sup>4</sup> However, toxicity from these higher doses delayed therapy.<sup>1</sup> Therefore, better 1-year survival was observed with low-dose RD (96.5%) than with higher-dose RD (86%). The 24-month survival rate was 91% and 80% for the low- and high-dose RD regimens, respectively.<sup>5</sup>

**Bortezomib Combinations for Induction Therapy.** Combinations of bortezomib plus established drugs such as melphalan-prednisone, dexamethasone, and doxorubicin and, more recently, with TD and RD, are providing superior efficacy compared with previous standards of care. These regimens exhibit therapeutic activity across various front-line populations, including patients with renal impairment, high-risk cytogenetics (eg, Del 13q and Del 17p), and advanced bone disease.<sup>6</sup>

**BD vs VAD.** Interim analysis of the phase III trial by the Intergroupe Francophone du Myelome (IFM) reported CR, nCR, and VGPR rates of 9%, 20%, and 23%, respectively, for bortezomib plus dexamethasone (BD) and of 4%, 9%, and 17% for VAD.<sup>7</sup> These results indicated a clear advantage in the use of bortezomib during induction. The only limitation with the BD regimen was a high incidence of grade 2 to 4 peripheral neuropathy (grade 2, 25%; grade 3 to 4, 7%).<sup>7</sup>

**PAD vs VAD.** In a small initial study comparing PAD with VAD, the PAD regimen resulted in a 24% CR rate (5% for nCR) and a 95% ORR.<sup>2</sup> In the large, follow-up, phase III trial (HOVON-65/GMMG-HD4), interim analysis showed rates of CR, VGPR or better, and partial response (PR) or better of 5%, 41%, and 80%, respectively, for the PAD arm and of 0%, 17%, and 64% for the VAD arm.<sup>8</sup> With maintenance therapy, the CR rate was 27% in the PAD arm and 5% in the VAD arm.

**VTD vs TD.** VTD combination therapy for up to 4 cycles resulted in an 18% CR rate and an ORR of 92%.<sup>9</sup> The incidence of peripheral neuropathy of grade 3 or greater was surprisingly low (8%). Myelosuppression and infection occurred in 8% of patients. A phase III trial demonstrated that VTD produced higher response rates compared with TD (**Table 1**).<sup>10</sup> Thrombotic events, constipation, somnolence, infection, and neuropathy are the most common adverse events associated with thalidomide use.<sup>11</sup>

<b>Table 1. Response rates from VTD and TD induction</b>			
<b>Response</b>	<b>Rate of Response (%)</b>		
	<b>VTD (n=226)</b>	<b>TD (n=234)</b>	<b>P value</b>
CR/nCR	33	12	<.001
≥VGPR	61	30	<.001
≥PR	92	79	<.001

Data from Cavo.<sup>10</sup>

**RVD.** Combination therapy using both lenalidomide and bortezomib with dexamethasone resulted in an ORR of 100%, including a 74% rate for VGPR or better and a 44% rate for CR/nCR.<sup>12</sup> Efficacy was independent of baseline cytogenetics. Median duration of response was 2.8 months. The most common grade 3 adverse events included metabolic alterations (9%); hypophosphatemia (8%); pneumonia, liver function change, and infection (5% each); and peripheral neuropathy, dizziness, cardiac problems, and anemia (3% each).

---

## Conditioning Regimens for Transplantation

---

Single-agent melphalan is the best high-dose conditioning regimen for patients with multiple myeloma undergoing ASCT. Typical conditioning regimens include melphalan with or without total body irradiation or melphalan alone. The IFM 9502 study showed that, compared with melphalan plus total body irradiation, melphalan alone resulted in faster hematologic recovery from neutropenia and thrombocytopenia and lower transfusion requirements.<sup>13</sup> Melphalan alone was also associated with a reduced incidence of grade 3 or 4 mucositis, shorter duration of use of intravenous antibiotics, and shorter hospital stays. In addition, there was a survival advantage for melphalan alone compared with melphalan plus total body irradiation (65.8% vs 45.5%). Melphalan as a single agent can also be used for patients with renal insufficiency.

---

## Stem Cell Transplantation

---

Various types of HDT-ASCT procedures are used in the treatment of patients with multiple myeloma. These

include a single ASCT, tandem SCT, and allogeneic SCT (allo-SCT), which is treatment with HDT followed by SCT from HLA-matched donors. Allo-SCT can be done with myeloablative or nonmyeloablative therapy. Nonmyeloablative therapy is a technique designed to decrease the toxicity of allo-SCT but preserve the graft-versus-myeloma effect. Allo-SCT can also follow ASCT.<sup>5</sup>

**Patient Selection.** Appropriate patients for SCT are those with a good ECOG performance status (grade <2) who have no significant coexisting illnesses (eg, cardiomyopathy; pulmonary, liver, or neurologic dysfunction; or renal insufficiency).<sup>14</sup> The risks and benefits of SCT need to be weighed on an individual basis. Patients with renal insufficiency need to be carefully evaluated, but they are not automatically excluded.

***Appropriate patients for SCT are those with a good ECOG performance status (grade <2) who have no significant coexisting illnesses.***

**Timing of SCT.** There are 2 strategic approaches for the timing of SCT. In the “early” strategy, the transplant is done immediately after induction therapy, regardless of the patient’s response to induction. In the “late” strategy, stem cells are collected and stored after induction. Induction is continued in patients achieving a PR or better until they reach a response plateau. The patient is then observed and, upon relapse, is treated with additional cycles of therapy and then transplanted. Fermand and colleagues studied outcomes with the early and late approaches.<sup>15</sup> OS was similar for patients transplanted either early or late. However, patients treated using the early strategy had a longer time without symptoms, which may suggest that these patients have a better quality of life and receive less chemotherapy overall. Patients treated with early SCT also may receive less alkylator therapy and therefore have a lower risk of developing myelodysplastic syndrome or secondary leukemia.

**Stem Cell Mobilization.** Mobilization using a cytokine-only approach is well tolerated, but its utility is limited by suboptimal stem cell yields in some patients. The addition of a chemotherapeutic agent improves stem cell yield by 2- to 5-fold, although it increases toxicity, morbidity, and resource utilization. The target for CD34+ cell collection for a single ASCT is generally 4 to 6 x 10<sup>6</sup> CD34+ cells/kg. Engraftment is delayed once the cell yield falls below 2 x 10<sup>6</sup> CD34+ cells/kg.<sup>16</sup> Increasing the CD34+ cell yield is associated with faster and more durable recovery of neutrophils and platelets, and it may be associated with improved survival. Insufficient mobilization occurs in 5% to 30% of patients, necessitating additional mobilization attempts or precluding transplantation for that person. Novel agents are being developed to amplify CD34+ yields without introducing additional toxicity.<sup>17</sup>

Plerixafor (sc) is newly approved for stem cell mobilization and augments the effects of granulocyte–colony stimulating factor (G-CSF). It blocks the binding between chemokine receptor 4, found on CD34+ cells, and its ligand, stromal cell–derived factor-1. Use of plerixafor together with G-CSF results in mobilization of a greater number of CD34+ cells than with G-CSF alone. Time to engraftment and graft durability are similar for cells harvested using plerixafor plus G-CSF or G-CSF alone.<sup>18</sup>

**Stem Cell Collection.** Neither bortezomib nor thalidomide regimens have an adverse impact on the

ability to harvest stem cells. Lenalidomide, however, may result in lower stem cell yields, although it is difficult to compare the yields reported in different studies because of differences in treatment duration, age of the patient undergoing SCT, type of mobilization regimen, and collection target. [2,16](#) The International Myeloma Working Group recommends early mobilization of stem cells, preferably within the first 4 cycles of therapy, in patients treated with these novel induction agents.[16](#)

**Effect of Improved Induction Regimens on Need for ASCT.** Although the use of newer drugs for induction has resulted in improved efficacy in multiple myeloma, none of these drugs is a cure. Therefore, ASCT is still needed, as clinical trial data are lacking on the comparative survival effect of newer induction regimens with and without HDT-ASCT. [1,19](#) For patients who are suitable candidates for transplantation, ASCT after induction therapy improves response rates, PFS, and OS compared with conventional chemotherapy. Patients who were in nCR at the time of transplant, and converted to CR after ASCT, had better survival, which suggests that reducing minimal residual disease improves overall outcome.[2](#)

**Standard-Dose vs High-Dose Chemotherapy.** A comparison of survival time for patients treated with standard-dose chemotherapy vs HDT-SCT as a function of disease stage is shown in [TABLE 2,20](#) For all 3 disease stages, HDT-SCT results in significantly longer survival time, with median survival increasing by 56 months for stage 1 patients, 28 months for stage 2 patients, and 20 months for stage 3 patients.

<b>Table 2. Median survival for patients treated with standard- or high-dose chemotherapy (HDT)</b>		
	<b>Median Survival (months)</b>	
	<b>Chemotherapy</b>	<b>HDT-SCT</b>
<b>Stage 1</b>	55	111
<b>Stage 2</b>	40	68
<b>Stage 3</b>	25	45

Data from Greipp.[20](#)

As previously noted, one way to improve outcomes of transplantation is to utilize more effective induction regimens. A few trials have reported comparisons of combination induction regimens that incorporate thalidomide and bortezomib with more traditional drug combinations, such as VAD in patients proceeding to transplantation. [TABLE 3](#) shows the major response rates after induction and again after transplantation, as well as survival outcomes for various induction regimens. [21-24](#)

**Table 3. Response rates from novel drug combinations in patients proceeding to ASCT**

Reference	No. of Patients	Induction Regimens	Major Response After				Survival at (year)
			Induction %		Autograft %		
			≥nCR	≥VGPR	≥nCR	≥VGPR	
Harousseau et al <sup>21</sup>	240	Bortezomib, dex	21	47	35	62	92% (1.5)
	242	Vincristine, dex, adriamycin	8	19	24	42	89% (1.5)
Cavo et al <sup>22</sup>	74	Bortezomib, thalidomide, dex	36	60	57	77	NR
	79	Thalidomide, dex	9	27	28	54	
Rajkumar et al <sup>23</sup>	102	Lenalidomide, low or high dex->ASCT					94% (2) <sup>a</sup>
	91	Lenalidomide, high dex	4 <sup>b</sup>	52	NR	NR	80% (2)
	120	Lenalidomide, low dex	2 <sup>b</sup>	44			91% (2)
Macro et al <sup>24</sup>	100	Thalidomide, dex	NR	25	NR	44%	NR
	104	Vincristine, dex, adriamycin		7		41%	

ASCT, autologous stem cell transplantation; CR, complete response; dex, dexamethasone; NR, not reported.

<sup>a</sup>Only these patients received stem cell transplant (not randomized); others remained on induction regimen.

High dex=480 mg/cycle; low dex=160 mg/cycle.

Bone marrow examinations were not required in the study for confirmation of CR.

Reprinted with permission from Bensinger W. *Leukemia*. 2009;23:442-448.<sup>5</sup>

**Single vs Double ASCT.** Double-intensive therapy with 2 successive ASCTs prolongs response duration. The largest study (IFM 94), with a 6.2-year follow-up after randomization, demonstrated that 2 successive ASCTs, each preceded by HDT, provided significant benefit compared with a single transplantation after HDT. In the single-transplant group, the probability of event-free survival (EFS), relapse-free survival (RFS), and OS at 7 years postdiagnosis was 10%, 13%, and 21%, respectively. In the double-transplant group, the EFS, RFS, and OS probabilities at 7 years were 20%, 23%, and 42%, respectively. Median EFS and OS were 2.1 and 4 years, respectively, for single ASCT and 2.5 and 4.8 years, respectively, for double ASCT. A CR/VGPR was achieved by 42% and 50% of patients in the single-transplant and double-transplant groups, respectively.<sup>25</sup>

**Tandem ASCT.** In the Total Therapy 2 (TT2) trial, tandem ASCT with or without thalidomide for induction, consolidation, and maintenance has resulted in 5-year estimated OS and EFS of 66% and 51%, respectively.<sup>26</sup> Two-thirds of patients without cytogenetic abnormalities were alive at 7 years. The duration of complete remission at 7 years in patients with cytogenetic abnormalities was also improved; 45% of patients remained relapse free in the thalidomide-treated cohort, compared with 20% in the control arm (no thalidomide). When bortezomib was incorporated into up-front therapy in a tandem-transplant regimen for newly diagnosed multiple myeloma (TT3 trial), 92% of patients achieved CR and sustained that remission for 2 years.<sup>27</sup> The 92% CR rate in TT3 was superior to the 81% CR rate with thalidomide in the TT2 trial. EFS was also better in TT3, and patients in this trial also showed a trend for improved OS. An important finding in this trial is that bortezomib prolonged CR, EFS, and OS even in the traditionally unfavorable FGFR23/MMSET subgroup.

**Post-Transplantation Response With New Induction Regimens.** Effective combinations of novel induction agents can have a remarkable impact on both pre- and post-ASCT clinical outcome. In the phase III IFM study that compared BD with VAD, 78% of BD-induced patients achieved a VGPR or better after ASCT, compared with 55% of VAD-induced patients. Infection, neuropathy, and constipation were the most common toxicities with BD use.<sup>7</sup>

The Italian Myeloma Network GIMEMA has demonstrated that VTD induction in preparation for, and as consolidation after, melphalan monotherapy–based double ASCT resulted in higher rates of response (CR + nCR, 32% vs 12%; VGPR, 61% vs 30%) than the more commonly used TD.<sup>10</sup> Peripheral neuropathy of grade 3 or greater and skin rash were more frequent with VTD than TD (peripheral neuropathy, 9% vs 2.5%; skin rash, 7.5% vs 1%). The rates of high-quality responses in the VTD arm were significantly higher than in the TD arm, including CR (41% vs 20%), CR + nCR (54% vs 29%), and VGPR or better (75% vs 53%). After a median follow-up of 15 months, PFS was significantly better with VTD than with TD (20-month estimate: 93% vs 86%).

A phase III study by the Spanish Myeloma Group (PETHEMA/GEM) compared TD vs VTD vs VBMCP/VBAD/Velcade® in patients ≤65 years old with newly diagnosed symptomatic multiple myeloma.<sup>28</sup> Induction was followed by ASCT and melphalan 200 mg/m<sup>2</sup>. The CR rate was significantly higher with VTD (31%) and with VBMCP/VBAD/ Velcade® (22%) compared with TD (6%). The post-ASCT CR rate was also higher with VTD (50%) and with VBMCP/VBAD/Velcade® (39%) than with TD (26%). This analysis shows that including bortezomib in the VTD regimen and in the VBMCP/VBAD regimen results in a higher CR rate compared with TD, both before and after ASCT. As in the GIMEMA study described above, toxicity in the 3 arms of this PETHEMA/GEM study was not significantly different.

**Allogeneic SCT.** Allo-SCT is the only potentially curative modality for patients with multiple myeloma. The curative potential of this procedure is attributed to a graft-versus-tumor effect. The high-intensity conditioning regimen used results in sufficient cytoreduction and immune-suppression to allow the donor graft to establish. Allo-SCT also avoids the contamination of reinfused autologous tumor cells, a theoretical cause of relapse. The need for a suitable donor and the high transplant-related mortality (25% to 50%) with allo-SCT currently limits its wider use.<sup>29</sup>

In an effort to reduce transplant-related mortality, reduced-intensity (nonmyeloablative) conditioning (RIC) regimens have been used, with the intention of achieving immunosuppression rather than cytoreduction and to enable donor engraftment while minimizing toxicity and damage to normal tissues. RIC has been shown to produce reliable donor engraftment with relatively low mortality compared with high-dose regimens, and it minimizes toxicity and tissue damage. RIC conditioning should decrease the period of pancytopenia and reduce the high transplant-related mortality. With RIC conditioning for allo-SCT, mortality drops to 25% to 50%, although CR rates are lower, and there is a higher rate of disease progression compared with ablative regimens, as well as higher relapse rates and lower OS (TABLE 4).<sup>29-31</sup>

**Table 4. Comparison of TRM, PFS, and OS in patients treated with HDT allo-SCT and reduced-intensity conditioning allo-SCT**

	Treatment-Related Mortality (months)	3-Year PFS	3-Year OS
<b>HDT</b>	30%-50%	34%	51%
<b>Reduced-Intensity</b>	17%-41%	19%	38%

Data from Siddiqui.<sup>31</sup>

**Strategies to Improve Allo-SCT Outcomes.** Potential methods to improve outcomes from allo-SCT have been investigated. These include intermediate-intensity, yet nonmyeloablative, conditioning regimens; tandem transplants; and use of peripheral blood cells. Other approaches involve graft engineering to improve graft-vs-myeloma activity while reducing graft-versus-host disease (GVHD), and the use of maintenance therapy post-transplant. Conditioning regimens using targeted therapies (eg, bone-seeking radioisotopes) have also been studied.<sup>2,5</sup>

**Tandem or Repeat Stem Cell Transplants.** Tandem ASCT/allo-SCT is a promising treatment option to reduce relapse for patients with advanced multiple myeloma. ASCT is followed 2 to 6 months later by RIC for allo-SCT (ASCT/allo-SCT), thereby providing temporal separation between tumor reduction by HDT and the graft-vs-myeloma effect. Rotta et al studied tandem ASCT or allo-SCT performed within 10 months of initial therapy (median, 7 months). The allograft conditioning regimen utilized high-dose melphalan; autograft was followed by 2 Gy total body irradiation for all patients (some patients received fludarabine), after which allo-SCT was performed. Postgraft immunosuppression was provided by cyclosporine or tacrolimus and mycophenolate mofetil.<sup>32</sup> At allo-SCT, the CR rate was 21%, VGPR rate was 22%, and PR rate was 41%; 14% of patients had refractory disease and 2% had progressive disease. All patients achieved sustained donor engraftment. Grade 2 to 4 acute GVHD occurred in 42% of the patients, and 74% had extensive chronic GVHD. ORR was 94%, with 65%, 11%, and 19% of patients achieving CR, VGPR, and PR, respectively (**TABLE 5**).

**Table 5. Responses from tandem auto/allo transplants**

	Best Response After AlloHCT		At AutoHCT		At AlloHCT	
	Pts, n	%	Pts, n	%	Pts, n	%
CR	66	65	7	7	19	18
VGPR	11	11	19	18	24	23
PR	19	19	52	50	41	40
RD/SD	4	4	17	16	16	16
PD	2	2	10	10	2	3
<b>Total</b>	<b>102</b>	<b>100</b>	<b>105</b>	<b>100</b>	<b>102</b>	<b>100</b>

This research was originally published in *Blood*. Rotta M, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. 2009;113(14):3383-3391.<sup>33</sup>

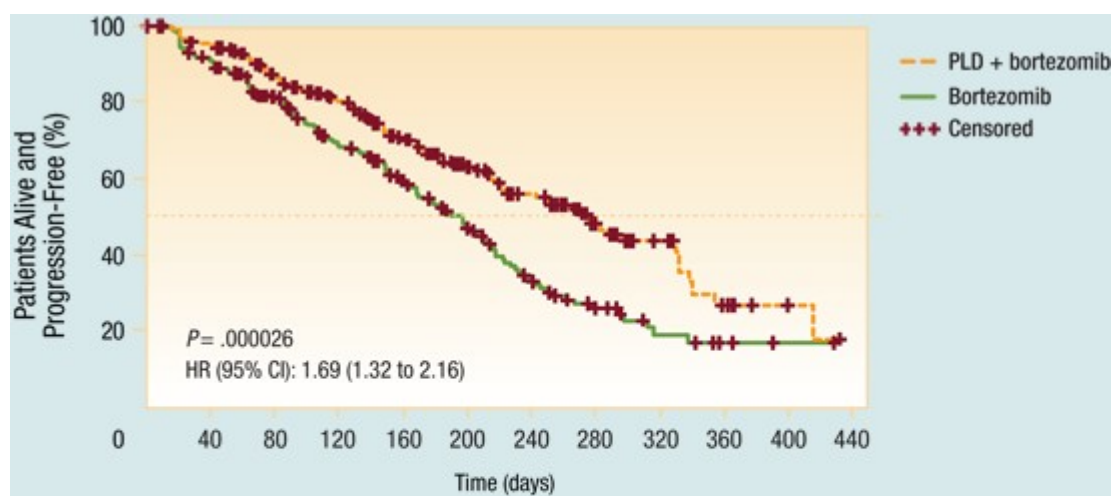
After a median follow-up of 6.3 years from allografting, median time to progression (TTP) was 5 years. Median OS was not reached, and median PFS was 3 years. At 5 years, OS and PFS were 64% and 36%, respectively. The cumulative incidence of nonrelapse mortality at 5 years was 18%. Most (95%) of the nonrelapse mortality was related to GVHD and/or infection.<sup>33</sup>

**Maintenance Therapy Following Transplantation.** Dexamethasone, interferon, and thalidomide have been studied for maintenance therapy in patients whose disease responds to ASCT or allo-SCT. Brinker and colleagues retrospectively reviewed the use of thalidomide maintenance therapy, started between 3 and 6 months after transplantation and continuing until toxicity precluded further therapy or until disease progression. Median survival was 65.5 months in patients receiving thalidomide maintenance, compared with 44.5 months in the no-maintenance group.<sup>34</sup> A study by Attal and coworkers also provided evidence of thalidomide's effectiveness as maintenance therapy following transplantation. Patients in this study received thalidomide plus pamidronate or pamidronate alone as maintenance therapy. The addition of thalidomide improved outcomes, as measured by CR/VGPR (67% vs 55%), 3-year EFS (52% vs 36%), 4-year probability of survival (87% vs 77%), and the proportion of patients who had skeletal events (18% vs 24%).<sup>35</sup> Thalidomide now carries a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) for maintenance therapy; thalidomide plus prednisone is a category 2A recommendation. Lenalidomide and bortezomib are also under investigation for maintenance therapy.

**Salvage Therapy.** Conventional-dose salvage therapy is considered in 3 clinical situations: (1) progressive disease following ASCT or allo-SCT, (2) primary progressive disease following initial auto-SCT or allo-SCT, and (3) progressing or relapsing disease in nontransplant patients after initial induction therapy.<sup>36</sup>

If the relapse occurs at more than 6 months after the initial induction is complete, patients may be re-treated with the same induction regimen.<sup>36</sup> Based on results from the phase III APEX trial,<sup>37</sup> bortezomib is an NCCN category 1 recommendation for salvage therapy. In the APEX study, median TTP was 6.2 months for patients receiving bortezomib plus dexamethasone and 3.5 months for those receiving dexamethasone alone.<sup>37</sup> Bortezomib plus dexamethasone also demonstrated higher response rates (CR + PR, 38% vs 18%) and improved 1-year survival (80% vs 66%). Median survival increased by 6 months, from 23.7 months for the dexamethasone alone group to 29.8 months for the patients receiving bortezomib plus dexamethasone.<sup>38</sup> Among responding patients, 56% had an improved response, with longer therapy beyond initial response, leading to continued improvement in overall quality of response.<sup>38</sup>

Bortezomib in combination with pegylated liposomal doxorubicin (PLD) has been approved by the Food and Drug Administration for the treatment of patients with multiple myeloma who have had at least one prior therapy but have not yet received bortezomib. In the MMY-3001 trial, the combination extended median TTP from 6.5 months for bortezomib alone to 9.3 months for the 2 drugs together.<sup>39</sup> The median duration of response increased from 7.0 to 10.2 months. **FIGURE 1** depicts the rate of PFS. Although bortezomib plus PLD is superior to bortezomib monotherapy for patients with relapsed/refractory disease, the combination regimen is associated with a higher incidence of grade 3/4 myelosuppression, constitutional symptoms, gastrointestinal, and dermatologic toxicities consistent with the known toxicities of the 2 agents individually.



**Figure 1**

Comparison of efficacy of bortezomib vs bortezomib + PLD in relapsed/refractory MM patients, as measured by the % of patients who were progression-free vs time post treatment

Kaplan-Meier plot of time to disease progression in patients treated with bortezomib or bortezomib plus PLD for relapsed/refractory multiple myeloma. HR, hazard ratio.

Reprinted with permission from Orlowski RZ, et al. *J Clin Oncol*. 2007;25:3892-3901.<sup>39</sup>

Lenalidomide in combination with dexamethasone is another NCCN category 1 recommendation for salvage therapy.<sup>36</sup> The North American MM-009 trial reported increased OS (29.6 vs 20.2 months) and increased median TTP (11.1 vs 4.7 months) in patients receiving the combination regimen as compared with those receiving dexamethasone alone.<sup>40</sup> Grade 3/4 adverse events were reported in 85.3% of patients in the lenalidomide-plus-dexamethasone group and in 73.1% of those treated with dexamethasone alone. These

events resulted in study discontinuation in 19.8% and 10.2% of patients, respectively. Grade 3/4 neutropenia, thrombocytopenia, and venous thromboembolism were more common in patients receiving the combination regimen. Neutropenia could be managed with administration of G-CSF, and thromboembolic events could be managed with anticoagulants. Similar results were obtained in the International MM-010 trial.<sup>41</sup> Other monotherapy regimens and combinations of a variety of agents have been investigated for salvage therapy, but bortezomib monotherapy, bortezomib plus PLD, and lenalidomide plus dexamethasone are the only approaches with an NCCN category 1 recommendation.

---

## Therapeutic Strategies Based on Comorbidities and Clinical Setting

---

**Patients With Comorbidities.** Because of their generally older age, patients with multiple myeloma frequently present with serious comorbidities such as renal impairment or diabetes. Loss of renal function affects drug clearance, leading to increased toxicity of commonly used drug regimens. It also limits choice of therapy or requires modification in dosing and schedule of administration. Some drug combinations exacerbate hyperglycemia. Therefore, patients with comorbidities pose a greater challenge to clinicians. The introduction of novel targeted therapies has broadened and improved the treatment options for all patients with multiple myeloma, including those with renal impairment. Bortezomib, in particular, is cleared independently of renal function. Bortezomib-based regimens induce rapid reversal of declining renal function. Clinical activity has been reported regardless of renal impairment in both newly diagnosed patients and those with relapsed/refractory disease. In contrast, lenalidomide is cleared largely via the kidney, and thus the dose must be dose-adjusted for patients who have significant renal dysfunction.<sup>42</sup>

***The introduction of novel targeted therapies has broadened and improved the treatment options for all patients with multiple myeloma, including those with renal impairment.***

Steroids are standard components of multiple myeloma therapy. Glucocorticoids, however, can increase insulin resistance and lead to the development of steroid-induced diabetes. Steroid-sparing and steroid-free regimens have been investigated in multiple myeloma patients who also have diabetes or are at risk for diabetes. An example of a steroid-free regimen is bortezomib plus PLD, which has proven highly efficacious (ORR, 44% vs 41% for bortezomib alone).<sup>43</sup> Another approach is a steroid-sparing regimen such as lenalidomide plus low-dose dexamethasone, given as a total of 160 mg instead of the standard 480 mg per cycle.<sup>44</sup> Approaches such as these are predicted to improve options for patients with diabetes.

In addition to the potential for increased toxicity from treatment, patients who have coexisting medical problems may have reduced quality of life after ASCT. High-dose therapy may not be beneficial for these patients. Decision tools may be helpful in predicting the risk of transplant-related toxicity and aid in identifying patients who are most, or least, suited for ASCT.<sup>45</sup>

**Management of the Elderly Myeloma Population.** The number of elderly patients with myeloma is expected to increase as the US population ages, which will translate into more complex and challenging treatment decisions in clinical practice. Currently, the 5-year survival rate is 42.9% for patients <65 years and 25.2% for patients ≥65 years of age; in patients ≥75 years of age, survival is dramatically decreased.<sup>46</sup> In an effort to improve survival outcomes in elderly patients, the use of HDT-ASCT in patients >70 years of age has been investigated. Some results suggest that the elderly exhibit similar toxicity profiles and achieve similar survival benefits as do younger patients. In one study, the median TTP after transplantation and the median OS from diagnosis was equivalent in patients >70 years old and in those <65 years old.<sup>47</sup> However, other randomized studies of HDT in elderly patients do not demonstrate survival benefits. The optimal therapy for elderly patients with multiple myeloma needs to be individualized, both to account for heterogeneity in baseline characteristics as well as to measure efficacy in terms of clinical outcomes relevant to this population. Such outcome measures include prevention of disability and quality of life.<sup>46</sup>

***The optimal therapy for elderly patients with multiple myeloma needs to be individualized, both to account for heterogeneity in baseline characteristics as well as to measure efficacy in terms of clinical outcomes relevant to this population.***

Patient selection among the elderly is vitally important in order to identify patients most likely to tolerate ASCT and benefit from it. Patient selection algorithms that incorporate measures of transplant-specific comorbidity, cognitive function, baseline physiologic performance, and self-reported psychosocial function will need to be developed and validated. Patient stratification based on these factors, indicative of physiologic age, is more relevant than categorization based on chronologic age.

Preparative and conditioning regimens that are maximally effective and minimally toxic in an older population need to be further developed. Specific agents to be used and dosing strategies for induction therapy, conditioning, and post-transplant maintenance therapy also need to be established. In particular, dose reduction of melphalan should be considered in this population.

---

## Conclusion

---

Important progress has been made in the treatment of multiple myeloma with the use of new drugs and combinations and new approaches to ASCT, including reduced-intensity allografts. Despite these advances, multiple myeloma remains an incurable disease for the majority of patients. Patient outcomes, particularly in poor-prognosis disease, need to be improved. Ongoing clinical trials with bortezomib, thalidomide, and lenalidomide will continue to provide valuable data for determining whether these drugs contribute to longer survival and extended disease control. The challenge at present is how to optimize mobilization and collection of stem cells and integrate the best combinations of new and old drugs in the multiple phases of therapy for this hematologic malignancy.

---

## References

---

1. Bensinger W. Stem cell transplantation for multiple myeloma in the era of novel drugs. *J Clin Oncol*. 2008;26:480-492.
2. Bensinger W. Initial therapy of multiple myeloma in patients who are candidates for stem cell transplantation. *Curr Treat Options Oncol*. 2007;8:135-143.
3. Lacy M, Gertz M, Dispenzieri A, et al. Lenalidomide plus dexamethasone (Rev/Dex) in newly diagnosed myeloma: response to therapy, time to progression, and survival [abstract]. *Blood*. 2006;108(part 1):239a.
4. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2007;25 (suppl):Abstract LBA8025.
5. Bensinger W. Role of autologous and allogeneic stem cell transplantation in myeloma. *Leukemia*. 2009;23(3):442-448.
6. Richardson PG, Mitsiades C, Schlossman R, et al. Bortezomib in the front-line treatment of multiple myeloma. *Expert Rev Anticancer Ther*. 2008;8(7):1053-1072.
7. Harousseau J-L, Marit G, Caillot D, et al. VELCADE/dexamethasone (VelDex) versus VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): an interim analysis of the IFM 2005-01 randomized multicenter phase III trial [abstract]. *Blood*. 2006;108(part 1):21a.
8. Sonneveld P, van der Holt B, Schmidt-Wolf IGH, et al. First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycin, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM). *Blood*. 2008;112:Abstract 653.
9. Wang S, Yang J, Quian J. Tumor evasion of the immune system: inhibiting p38 MAPK signaling restores the function of dendritic cells in multiple myeloma. *Blood*. 2005;107:2432-2439.
10. Cavo M, Tacchetti P, Patriarca F, et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. *Blood*. 2008;112:Abstract 158.
11. Cavo M, Di Raimondo F, Zamagni E, et al. Short-term thalidomide incorporated into double autologous stem-cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. *J Clin Oncol*. 2009; ePub ahead of print.
12. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple

- myeloma: final time-to-event results of the APEX trial. *Blood*. 2007;110:3557-3560.
13. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m<sup>2</sup> melphalan and 8 Gy total body irradiation plus 140 mg/m<sup>2</sup> melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood*. 2002;99:731-735.
  14. Harousseau J-L, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2009;360:2645-2654.
  15. Fermand JP, Ravaud P, Chrevet S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood*. 1998;92:3131-3136.
  16. Kumar S, Giral S, Stadtmauer EA, et al, on behalf of the International Myeloma Working Group (IMWG). Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. *Blood*. 2009;114(9):1729-1735.
  17. Bensinger W, DiPersio JF, McCarty JM. Improving stem cell mobilization strategies: future directions. *Bone Marrow Transplant*. 2009;43(3):181-195.
  18. Wagstaff AJ. Plerixafor in patients with non-Hodgkin's lymphoma or multiple myeloma. *Drugs*. 2009;69(3):319-326.
  19. Jagannath S. New drugs in multiple myeloma and the significance of autologous stem cell transplants. *Clin Adv Hematol Oncol*. 2009;7(3):178-179.
  20. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412-3420.
  21. Harousseau JL, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): updated data from IGM 2005/01 trial [abstract 8505]. *J Clin Oncol*. 2008;26(part 1):455S.
  22. Cavo M, Patriarca F, Tacchetti P, et al. Bortezomib (Velcader)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (VD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM) [Abstract 73]. *Blood*. 2007;110(I part 1):30A.
  23. Rajkumar SV, Jacobus S, Callander N, et al. Randomized trial of lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: analysis of response, survival, and outcome [Abstract 8504]. *J Clin Oncol*. 2008;26(part 1):455S.
  24. Macro M, Divine M, Uzunhan Y, et al. Dexamethasone+thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): a randomized trial [Abstract 57]. *Blood*. 2008;108(part 1):22a.
  25. Attal M, Harousseau J-L, Facon T, et al, for the InterGroupe Francophone du Myelome. New drugs in multiple myeloma and the significance of autologous stem cell transplants. *N Engl J Med*. 2003;349:2495-2502.
  26. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*.

- 2008;112:3115-3121.
27. Pineda-Roman M, Zangari M, Haessler J, et al. Sustained complete remission in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. *Br J Haematol*. 2008;140:625-634.
  28. Rosinol L, Cibeira MT, Martinez J. Thalidomide/dexamethasone (TD) vs bortezomib (Velcade®)/Thalidomide/dexamethasone (VTD) vs VBMCP/VBAD/Velcade® as induction regimens prior autologous stem cell transplantation (ASCT) in younger patients with multiple myeloma (MM): first results of a prospective phase III PETHEMA/Gem Trial. *Blood*. 2008;112:Abstract 654.
  29. Bensinger W. Is there still a role for allogeneic stem cell transplantation in multiple myeloma? *Best Pract Res Clin Haematol*. 2007;20(4):783-795.
  30. Cole SM, Saliba R, Pelosini M, et al. Reduced-intensity regimens for allogeneic stem cell transplantation improve the outcome in advanced multiple myeloma. Abstract presented at: 50th ASH Annual Meeting and Exposition; December 6-9, 2008; San Francisco, California; Abstract 3298.
  31. Siddiqui M, Gertz M. The role of high-dose chemotherapy followed by peripheral blood stem cell transplantation for the treatment of multiple myeloma. *Leuk Lymphoma*. 2008;49(8):1436-1451.
  32. Rotta M, Storer B, Sahebi F, et al. Tandem auto/alloHCT for newly diagnosed multiple myeloma (MM) patients. Abstract presented at: 50th ASH Annual Meeting and Exposition; December 6-9, 2008; San Francisco, California; Abstract 1130.
  33. Rotta M, Storer BE, Sahebi F, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood*. 2009;113(14):3383-3391.
  34. Brinker BT, Waller EK, Sahebi F, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer*. 2006;106:2171-2180.
  35. Attal M, Harousseau J-L, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108(10):3289-3294.
  36. NCCN Practice Guidelines in Oncology-v.2.2010. Multiple myeloma. Available at: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed October 21, 2009.
  37. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487-2498.
  38. Richardson PG, Sonneveld P, Schuster MW, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood*. 2007;110(10):3557-3560.
  39. Orłowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25:3892-3901.
  40. Weber DM, Chen C, Niesvizky R, et al, for the Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-

2142.

41. Dimopoulos M, Spencer A, Attal M, et al, for the Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2123-2132.
42. Jagannath S. Treatment of patients with myeloma with comorbid conditions: considerations for the clinician. *Clin Lymphoma Myeloma*. 2008; 8(suppl 4):S149-S156.
43. Blade J, San Miguel JF, Nagler A, et al. The prolonged time to progression with pegylated liposomal doxorubicin + bortezomib versus bortezomib alone in relapsed or refractory multiple myeloma is unaffected by extent of prior therapy or previous anthracycline exposure [Abstract 410]. *Blood*. 2007;111:127a.
44. Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [Abstract 74]. *Blood*. 2007;111:131a.
45. Labonté L, Iqbal T, Zaidi MA, et al. Utility of comorbidity assessment in predicting transplantation-related toxicity following autologous hematopoietic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14(9):1039-1044.
46. Klepin HD, Hurd DD. Autologous transplantation in elderly patients with multiple myeloma: are we asking the right questions? *Bone Marrow Transpl*. 2006;38:585-592.
47. Kumar SK, Dingli D, Lacy MQ. Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: results from a matched pair analysis. *Am J Hematol*. 2008;83:614-617.

This initiative is supported by educational grants from:

Millennium Pharmaceuticals, Inc.



Postgraduate Institute  
for Medicine



In collaboration with:



ANNENBERG CENTER  
FOR HEALTH SCIENCES  
AT EISENHOWER