Clinical Impact of Bortezomib in Frontline Regimens for Patients with Multiple Myeloma

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Key Words. Bortezomib • Combination regimen • Induction therapy • Multiple myeloma • Proteasome inhibitor • Stem cell transplantation

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the efficacy of bortezomib as part of primary therapy for patients with multiple myeloma.
2. Describe the safety of bortezomib and bortezomib-based regimens in patients with previously untreated multiple myeloma.
3. Identify new management options for patients with treatment-naïve multiple myeloma.

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ABSTRACT

Standard frontline therapy for multiple myeloma comprises cytoreductive therapy with or without consolidative high-dose therapy plus stem cell transplantation (HDT-SCT). Despite therapeutic advances, the disease remains incurable; most patients relapse following frontline treatment and die within 5 years of diagnosis. New options are required to enhance and prolong response, and improve survival, particularly for elderly patients and those with renal dysfunction. Preclinical studies have demonstrated the ability of bortezomib to enhance the activity of commonly used myeloma agents, an observation validated through clinical studies in both the relapsed and frontline settings. This review focuses on the growing body of clinical evidence showing the effectiveness of bortezomib and bortezomib-based combinations in newly diagnosed patients, characterized by high overall response rates and consistently high rates of complete response. A number of studies incorporating bortezomib as part of induction therapy have demonstrated no adverse impact of bortezomib on stem cell harvest and engraftment in patients proceeding to transplantation. The higher rates of complete response typically associated with bortezomib treatment may potentially improve clinical outcomes in this setting. Final results from ongoing phase III studies of bortezomib-based combinations versus standard regimens will help define the optimal use of bortezomib as a standard component of frontline therapy for multiple myeloma. The Oncologist 2007;12:978–990

Disclosure of potential conflicts of interest is found at the end of this article.
INTRODUCTION

Multiple myeloma is the second most common hematologic malignancy after non-Hodgkin’s lymphoma, with 10,790 deaths estimated in the U.S. in 2007 [1] and 19,200 deaths in the European Union in 2004 [2]. The disease remains incurable; most patients relapse following frontline treatment and die within 5 years of diagnosis [3]. Current treatment options for newly diagnosed patients include cytoreductive therapy with or without consolidative high-dose therapy (usually melphalan, 200 mg/m²) plus stem cell transplantation (HDT-SCT). Commonly accepted induction regimens include melphalan plus prednisone (MP); vincristine, doxorubicin, and dexamethasone (VAD); dexamethasone; and thalidomide plus dexamethasone [4]. Earlier studies demonstrated an overall survival (OS) and progression-free survival (PFS) benefit with HDT-SCT compared with conventional chemotherapy, plus higher overall response rates (ORRs; complete response [CR] plus partial response [PR]) and CR rates [5, 6]; with the use of novel combinations, both options seem comparable in terms of OS [7, 8].

Achieving CR is clinically relevant as it has been shown to be associated with better transplant outcome and longer survival post-transplant [6, 9–12]. Therefore, new frontline treatment options with the ability to deliver enhanced quality of response, including higher CR rates, are required. This may ultimately improve survival.

New treatment options are particularly important for elderly patients, those with renal dysfunction, and patients not eligible for HDT-SCT, for whom current treatment options are limited [13–17]. In addition, patients with poor prognostic markers such as elevated β2-microglobulin [18–20], high plasma cell labeling index [19, 21], or chromosome 13 deletion [18, 22] may also benefit from novel treatment options, which may overcome these poor prognostic factors.

Bortezomib (Velcade®; Millennium Pharmaceuticals Inc., Cambridge, MA, and Johnson & Johnson Pharmaceuticals, Research and Development, L.L.C., Raritan, NJ), a first-in-class proteasome inhibitor, is approved in the U.S. and European Union for the treatment of multiple myeloma patients who have received at least one prior therapy. The mechanisms of action of bortezomib include blocking of nuclear factor kappa B (NF-κB) activation [23, 24], which has been implicated in resistance to therapy [25, 26]. Figure 1 shows the mechanism of bortezomib in this pathway. Bortezomib was approved based on the results of the randomized, phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial [27, 28]. Compared with high-dose dexamethasone, single-agent bortezomib showed superiority in terms of response rates (including CR rates), median time to progression (TTP), and survival, and better quality of life [27–29]. This study also showed that a high quality of response (100% M-protein reduction) to bortezomib was associated with a longer duration of response [28]. In addition, bortezomib was well tolerated and retained its superiority over high-dose dexamethasone in elderly patients and patients with high-risk factors such as advanced disease, more prior lines of therapy, and refractoriness to prior therapy [30].

A subgroup analysis suggests that bortezomib may be more beneficial when used earlier in the course of treatment; in the APEX trial, patients with one prior line of therapy appeared to have a higher response rate, longer TTP, and longer survival following bortezomib treatment compared with patients with more than one prior line [28, 31]. In other studies in the relapsed setting, bortezomib has been shown to be active with a similar toxicity profile in patients with chromosome 13 deletion [32, 33], and in patients with renal dysfunction or renal failure requiring dialysis [34–36].

In addition to single-agent studies in the relapsed setting [27, 37, 38], bortezomib is also being investigated in a range of combination regimens with other antimyeloma agents [39], including steroids, melphalan, and immunomodulatory drugs (IMiDs) (Table 1) [40–58]. Encouragingly, despite patients having relapsed or refractory disease, high ORRs (up to 93%) [58] and CR/near complete response (nCR) rates (up to 64%) [58] have been reported.

The rationale for these studies was provided by the results of preclinical studies, which have shown that, in addition to single-agent activity in human myeloma cell lines resistant to melphalan, doxorubicin, and dexamethasone [59], in vitro bortezomib enhances sensitivity to and overcomes chemoresistance to these agents. For example, a 1,000,000-fold increase in sensitivity to melphalan was seen in two melphalan-resistant cell lines with the addition of bortezomib [24]. Enhanced melphalan sensitivity in chemosensitive cells and primary patient cells [24, 60], as well as synergistic activity between bortezomib and melphalan [61], has also been seen. Similarly, a 100,000-fold increase in sensitivity to doxorubicin was seen in two doxorubicin-resistant cell lines, and synergistic activity was seen in cell lines and primary patient cells [24, 60]. Furthermore, additive activity has been demonstrated with bortezomib plus dexamethasone [59].

Together, the preclinical data and results from studies in the relapsed setting of bortezomib alone or in combination have led to the investigation of bortezomib in the frontline setting, both as a single agent and in combination. This review presents a summary of the available data.
BORTEZOMIB IN FRONTLINE THERAPY FOR MULTIPLE MYELOMA

To date, data from more than 900 patients have been reported from 15 clinical trials investigating the role of bortezomib, as a single agent and in combination with other agents, in the frontline treatment of multiple myeloma. The following section summarizes recent reports from these studies; efficacy and safety data are listed in Table 2.

**Single-Agent Bortezomib**

In a multicenter, open-label phase II trial, 66 patients with newly diagnosed, symptomatic multiple myeloma received single-agent bortezomib [62]. The ORR was 40%, with a 10% CR/nCR rate. Minimal response was seen in 22% of patients; 32% had stable disease. Just 6% of patients showed disease progression. The CR rate compares favorably with the 0% CR/nCR rate reported with other single agents, including dexamethasone [63, 64] and thalidomide [65], used to treat frontline myeloma. A preliminary time-to-event analysis has been completed for 34 of these 66 patients; the median duration of best response was 8.5 months, while the median TTP was 6 months. The safety profile was similar to that seen in studies in relapsed/refractory multiple myeloma, with no unexpected adverse events. While 58% of patients had treatment-emergent peripheral neuropathy, grade 3 or higher was observed in only 2%; the toxicity was reversible in the majority of patients for whom follow-up data were available. Notably, small-fiber peripheral neuropathy was observed at baseline in 50% of patients with neurophysiologic testing, suggesting that underlying small-fiber neuropathy may be more common in myeloma than previously appreciated [62].

A second phase II trial of single-agent bortezomib is ongoing in patients with high-risk multiple myeloma, defined as those with elevated β2-microglobulin, high plasma cell labeling index, or deletion of the long arm of chromosome 13 [66]. The ORR among 39 evaluable patients was 45%, including a 5% very good PR (VGPR) rate. The median PFS duration was 9.9 months, and the median OS time had not been reached [66].

**Bortezomib-Based Combination Therapy in Patients Not Proceeding to HDT-SCT**

**Bortezomib Plus MP in Elderly Patients**

A multicenter, phase I/II study of 60 elderly patients (aged ≥65 years) ineligible for HDT-SCT evaluated the addition of bortezomib to the MP regimen (VMP) [67]. Among 53 evaluable patients, VMP produced an ORR of 89%, including a 32% CR rate and an 11% nCR rate. Among patients...
achieving CR, half of those assessed had no malignant plasma cells detectable by multiparametric flow cytometry (sensitivity level of $10^{-4}$–$10^{-5}$), representing immunophenotypic minimal residual disease status. These response rates, among the highest reported with conventional therapy, compare very favorably with those for MP—35%–53% ORR, including a 1%–9% CR rate [68–71]. Response to VMP was rapid, with 70% of patients responding by completion of the first cycle. VMP also compares very favorably with MP historical control data in the context of the PFS rate (91% versus 66%), event-free survival (EFS) rate (83% versus 51%), and OS rate (90% versus 62%) at 16 months [67]. Notably, in 33 patients for whom cytogenetic data were available, response rates appeared comparable among patients with and without retinoblastoma gene deletion or immunoglobulin heavy-chain translocations, suggesting that the mechanism of action of bortezomib may overcome the adverse impact of these factors [67].

<table>
<thead>
<tr>
<th>Table 1. Studies of bortezomib-based combination regimens in the relapsed/refractory setting</th>
<th>ORR</th>
<th>CR/nCR</th>
<th>Time-to-event data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib + dexamethasone [41]</td>
<td>73%</td>
<td>7%</td>
<td>EFS, not reached; OS, not reached</td>
</tr>
<tr>
<td>Bortezomib + pegylated liposomal doxorubicin [42,50]</td>
<td>73%</td>
<td>36%</td>
<td>TTP, 9.3 mos; OS, 38.3 mos</td>
</tr>
<tr>
<td>Bortezomib + pegylated liposomal doxorubicin [51]</td>
<td>48%</td>
<td>14%</td>
<td>TTP, 9.3 mos; DOR, 12 mos; OS, not reached</td>
</tr>
<tr>
<td>Bortezomib + melphalan [43]</td>
<td>47%</td>
<td>15%</td>
<td>PFS, 8 mos</td>
</tr>
<tr>
<td>Bortezomib + methylprednisolone [44]</td>
<td>62%</td>
<td>7%</td>
<td>TTP, 6.6 mos; DOR, 6.7 mos; OS, 20.2 mos</td>
</tr>
<tr>
<td>Bortezomib + melphalan ± dexamethasone [57]</td>
<td>59%</td>
<td>12%</td>
<td>TTP, 10 mos</td>
</tr>
<tr>
<td>Bortezomib + thalidomide ± dexamethasone [45]</td>
<td>55%</td>
<td>16%</td>
<td>EFS, 9 mos; OS, 22 mos</td>
</tr>
<tr>
<td>Bortezomib + lenalidomide ± dexamethasone [53]</td>
<td>39%</td>
<td>6%</td>
<td>DOR, 8 mos</td>
</tr>
<tr>
<td>Bortezomib + pegylated liposomal doxorubicin + dexamethasone [46]</td>
<td>65%</td>
<td>22%</td>
<td>NR</td>
</tr>
<tr>
<td>Bortezomib + pegylated liposomal doxorubicin + thalidomide [56]</td>
<td>56%</td>
<td>22%</td>
<td>PFS, 10.9 mos; OS, 15.7 mos</td>
</tr>
<tr>
<td>Bortezomib + cyclophosphamide + dexamethasone [47]</td>
<td>82%</td>
<td>12%</td>
<td>EFS, 12 mos; OS, not reached</td>
</tr>
<tr>
<td>Bortezomib + cyclophosphamide + dexamethasone [54]</td>
<td>75%</td>
<td>31%</td>
<td>NR</td>
</tr>
<tr>
<td>Bortezomib + cyclophosphamide + prednisone [52]</td>
<td>84%</td>
<td>38%</td>
<td>PFS, not reached; 1-year PFS, 61%; OS, not reached; 1-year OS, 87% (data for higher/active dose levels)</td>
</tr>
<tr>
<td>Bortezomib + thalidomide + dexamethasone + zoledronic acid [58]</td>
<td>93%</td>
<td>64%</td>
<td>NR</td>
</tr>
<tr>
<td>Bortezomib + pegylated liposomal doxorubicin + thalidomide + dexamethasone [48]</td>
<td>74%</td>
<td>33%</td>
<td>PFS, not reached; OS, not reached</td>
</tr>
<tr>
<td>Bortezomib + doxorubicin + thalidomide + dexamethasone [49]</td>
<td>63%</td>
<td>25%</td>
<td>6-mo survival, 89%</td>
</tr>
<tr>
<td>Bortezomib + melphalan + prednisone + thalidomide [40]</td>
<td>67%</td>
<td>43% (CR + VGPR)</td>
<td>1-year PFS, 61%; 1-year OS, 84%</td>
</tr>
<tr>
<td>Bortezomib + melphalan + dexamethasone + thalidomide [55]</td>
<td>60%</td>
<td>11%</td>
<td>PFS, 9.5 mos</td>
</tr>
</tbody>
</table>

*Abbreviations: CR, complete response; DOR, duration of response; EFS, event-free survival; nCR, near CR; MTD, maximum-tolerated dose; NR, not reported; ORR, overall response rate (CR + PR); OS, overall survival; PFS, progression-free survival; PR, partial response; TTP, time to progression; VGPR, very good partial response.

*aM-protein reduction.
*bSouthwest Oncology Group criteria.
*cReported after one cycle of treatment.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Design</th>
<th>$n$ enrolled/evaluable</th>
<th>Efficacy</th>
<th>Key toxicity</th>
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<tbody>
<tr>
<td><strong>Single-agent bortezomib therapy</strong></td>
<td></td>
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<tr>
<td>Single-agent bortezomib [62]</td>
<td>Multicenter, phase II</td>
<td>66/63</td>
<td>PR or better, 40%; CR/CRi, 10%; TTP, 6 mos; DOR, 8.5 mos</td>
<td>Peripheral neuropathy, 58%; constipation, 57%; nausea, 48%; fatigue, 43%; rash, 33%</td>
</tr>
<tr>
<td>Single-agent bortezomib plus bortezomib maintenance; ECOG 2A02 [66]</td>
<td>Multicenter, phase II; high-risk patients</td>
<td>42/39</td>
<td>PR or better, 45%; CR/CRi, NR; PFS, 9.9 mos; OS, not reached</td>
<td>Grade ≥3 toxicities: fatigue, 32%; hyponatremia, 24%; thrombocytopenia, 21%; diarrhea, 20%; anemia, 19%; neutropenia, 16%; abnormal electrolytes, 16%; syncope, 6%; neuropathy, 5%; nausea, 5%; pain, 5%; infections, 5%; gastrointestinal pain, 5%; dyspnea, 5%</td>
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<tr>
<td><strong>Bortezomib-based combination therapy</strong></td>
<td></td>
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<tr>
<td>VMP; GEM/PETHEMA [67]</td>
<td>Multicenter, phase I/II, dose-escalation; elderly patients</td>
<td>60/53</td>
<td>PR or better, 89%; CR/CRi, 43%; 16-mo PFS, 91%; 16-mo EFS, 83%; projected 2-yr survival, 86%</td>
<td>Grade ≥3 toxicities: thrombocytopenia, 51%; neutropenia, 43%; peripheral neuropathy, 17%; diarrhea, 16%; infection, 16%; anemia, 10%; constipation, 8%; asthenia, 5%</td>
</tr>
<tr>
<td>Bortezomib ± dexamethasone [73]</td>
<td>Multicenter, phase II</td>
<td>50/49</td>
<td>PR or better, 88%; CR/CRi, 18%; estimated 1-yr/2-yr survival, 92%/85%; estimated 2-yr survival in HDT-SCT/non-HDT-SCT patients, 91%/81%</td>
<td>Grade ≥2 toxicities: sensory neuropathy/neuropathic pain, 37%; fatigue, 20%; constipation, 16%; nausea, 12%; neutropenia, 12%</td>
</tr>
<tr>
<td>Bortezomib plus dexamethasone; IFM [74]</td>
<td>Multicenter, phase II</td>
<td>52/48</td>
<td>PR or better, 67%; CR/CRi, 21%</td>
<td>Grade ≥3 toxicities: infection, 10%; peripheral neuropathy, 6%</td>
</tr>
<tr>
<td>Bortezomib plus dexamethasone; IFM [75]</td>
<td>Multicenter, phase III versus VAD</td>
<td>420/161</td>
<td>PR or better, 82%; CR/CRi, 20%</td>
<td>Neurologic toxicities, 27% (4% grade 3 or 4); fever/infection, 14%</td>
</tr>
<tr>
<td>Bortezomib alternating with dexamethasone; PETHEMA [76]</td>
<td>Multicenter, phase II</td>
<td>40/39</td>
<td>PR or better, 67%; CR/CRi, 13%</td>
<td>Grade 3 toxicities: neutropenia, 15%</td>
</tr>
<tr>
<td>PAD [77]</td>
<td>Multicenter, phase I/II</td>
<td>21</td>
<td>PR or better, 95%; CR/CRi, 29%</td>
<td>Grade ≥3 toxicities: infection, 14%; herpes zoster, 14%; line infection, 14%; peripheral neuropathy, 5%; neutropenia, 5%; nausea/vomiting, 5%; postural hypotension, 5%; atrial fibrillation, 5%; hyperglycemia, 5%</td>
</tr>
<tr>
<td>Reduced-dose PAD [78]</td>
<td>Multicenter, phase II</td>
<td>20/19</td>
<td>PR or better, 89%; CR/CRi, 16%</td>
<td>Grade ≥3 toxicities: liver function test, 15%; psychiatric, 10%; fatigue, 5%; thrombocytopenia, 5%; neutropenia, 5%; infection, 5%</td>
</tr>
</tbody>
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(continued)
Table 2. (Continued)

<table>
<thead>
<tr>
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<th>Efficacy</th>
<th>Key toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib plus liposomal doxorubicin; CALGB 10301 [79]</td>
<td>Multicenter, phase II</td>
<td>63/29</td>
<td>PR or better, 79%; CR/nCR, 28%</td>
<td>Grade ≥3 toxicities: neutropenia, 18%; fatigue, 16%; thrombocytopenia, 14%; sensory neuropathy, 13%; lymphopenia, 13%; anemia, 9%; hand–foot syndrome, 9%; syncope, 9%; motor neuropathy, 5%; dehydration, 5%; rash, 5%; weight loss, 5%; hypotension, 5%; diarrhea, 5%; nausea, 5%; infection, 5%; dyspnea, 5%</td>
</tr>
<tr>
<td>VDD [80]</td>
<td>Phase II</td>
<td>30/28</td>
<td>PR or better, 89%; CR/nCR, 32%</td>
<td>Grade ≥3 toxicities: fatigue, 14%; pneumonia, 11%; thrombocytopenia, 7%; DVT/PE, 7%; hand–foot syndrome, 7%; neutropenia, 4%; diarrhea, 4%</td>
</tr>
<tr>
<td>VTD [81]</td>
<td>Single-center</td>
<td>38</td>
<td>PR or better, 87%; CR/nCR, 16%</td>
<td>Grade ≥3 toxicities: myelosuppression, 11%; neuropathy, 5%; DVT/PE, 5%; dry skin/rash, 3%; infection, 3%</td>
</tr>
<tr>
<td>Bortezomib plus thalidomide [82]</td>
<td>Single-center, phase II</td>
<td>27/27</td>
<td>PR or better, 81%; CR/nCR, 22%</td>
<td>Peripheral neuropathy: grade 1 in 48%; grade 2 in 33%; grade 3 in 18%; no grade 4; other grade 3 toxicities: anemia, 7%; anorexia, 7%; herpes zoster infection, 7%</td>
</tr>
<tr>
<td>VDT-PACE [85]</td>
<td>Phase I, single-center</td>
<td>12</td>
<td>PR or better, 83%; CR/nCR, 17%</td>
<td>Grade ≥3 toxicities (cycle 1): neutropenia, 100%; thrombocytopenia, 58%; anemia, 42%; neutopenic fever, 25%; infection, 25%; thrombosis, 17%; hyperglycemia, 17%; syncope, 8%</td>
</tr>
<tr>
<td>TT3, incorporating VDT-PACE; UARK 2003–33 [86]</td>
<td>Phase II</td>
<td>303</td>
<td>CR/nCR at 24 mos, 83%; CR at 24 mos, 56%; 24-mo OS, 86%; 24-mo EFS, 84%</td>
<td>Grade ≥3 toxicities post-induction: peripheral neuropathy, 14%; DVT/PE, 11%; constipation/bowel obstruction, 5%</td>
</tr>
</tbody>
</table>

*Post-transplant response rate reported.

Abbreviations: CALGB, Cancer and Leukemia Group B; CR, complete response; DOR, duration of response; DVT/PE, deep vein thrombosis/pulmonary embolism; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GEM, Grupo Español de Mieloma; HDT-SCT, high-dose melphalan therapy plus autologous stem cell transplant; IFM, Intergroupe Francophone du Myélome; nCR, near CR; NR, not reported; OS, overall survival; PAD, bortezomib, doxorubicin, and dexamethasone; PETHEMA, Programa para el Estudio de la Terapéutica en Hematopatía Maligna; PFS, progression-free survival; PR, partial response; TT2 + T/TT3, total therapy 2 + thalidomide/total therapy 3; TTP, time to progression; UARK, University of Arkansas; VAD, vincristine, doxorubicin, and dexamethasone; VDD, bortezomib, liposomal doxorubicin, and dexamethasone; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VMP, bortezomib, melphalan, and prednisone; VTD, bortezomib, thalidomide, and dexamethasone.

A regimen of seven cycles of therapy was administered (>9 months), indicating good tolerability of the VMP regimen in this elderly population [67]. Toxicities were comparable with those seen in other major bortezomib trials.

Data from this phase I/II study of VMP also compare well with those from two recently completed phase III studies assessing MP plus thalidomide (MPT) [68, 72]. In the study of MPT versus MP by Palumbo et al. [68], the ORR and CR rate were 76% and 16%, respectively, with a 2-year EFS rate of 54%. Although frontline MPT was more effec-
tive than MP, a higher rate of grade ≥3 thromboembolism (12% versus 2%) was seen and the discontinuation rate as a result of adverse events was higher with MPT than with MP (13% versus 3%) [68]. Similar results have been reported by Facon et al. [72].

Bortezomib-Based Combinations as Induction Therapy Prior to HDT-SCT

An important clinical question is the role of bortezomib and bortezomib-based cytoreductive therapy prior to HDT-SCT. Several clinical studies have provided efficacy and safety data in this patient population.

**Bortezomib plus Dexamethasone**

High-dose dexamethasone is a commonly used agent in frontline multiple myeloma treatment, and three studies have investigated bortezomib plus dexamethasone in newly diagnosed patients. In a multicenter phase II trial, dexamethasone was added to bortezomib for patients achieving less than a PR after two cycles or less than a CR after four cycles. In 49 evaluable patients, the ORR was 88% with an 18% CR/nCR rate [73]. With a median follow-up time of 27 months, the median OS had not been reached; estimated 1- and 2-year survival rates were 92% and 85%, respectively. In total, 25 patients proceeded to HDT-SCT; transplantation was successful in all of these patients, with an estimated 91% post-transplant 2-year survival rate. Among patients not proceeding to HDT-ASCT, the estimated 2-year survival rate was 81% [73].

The Intergroupe Francophone du Myélome (IFM) has examined bortezomib in combination with dexamethasone as induction prior to HDT-SCT [74]. In this phase II trial, 48 patients who were candidates for HDT-SCT received bortezomib plus dexamethasone from the start of therapy. Stem cell collection was performed prior to cycle 4. The ORR was 67%, including a 21% CR/nCR rate, prior to transplant. Post-transplant, the ORR and CR/nCR rates increased to 90% and 33%, respectively. Overall, bortezomib plus dexamethasone was well tolerated; importantly, there were no thromboembolic events. Preliminary data from a large IFM phase III study of bortezomib plus dexamethasone versus VAD as induction therapy prior to HDT-SCT have been reported [75]. Following four cycles of induction, the CR/nCR rate was 20% with bortezomib plus dexamethasone compared with 9% with VAD; the CR/VGPR rate and ORR were 43% and 82%, respectively, with bortezomib plus dexamethasone, compared with 26% and 67%, respectively, with VAD [75]. As in the phase II study, bortezomib plus dexamethasone was generally well tolerated.

**Bortezomib Alternating with Dexamethasone**

The use of bortezomib and dexamethasone has also been investigated in a phase II study in which the agents were used alternately in six 3- or 4-week cycles, with bortezomib administered in cycles 1, 3, and 5, and dexamethasone administered in cycles 2, 4, and 6 [76]. The ORR among 39 evaluable patients was 67%, including a 13% CR/nCR rate. There was no statistically significant difference in M-protein decrease during the bortezomib cycles and during the dexamethasone cycles [76]. Toxicities were mainly grade 1 or 2 [76].

**Bortezomib in Combination with Doxorubicin and Dexamethasone**

Oakereve et al. [77] investigated the addition of doxorubicin to bortezomib and dexamethasone (PAD) as induction therapy prior to HDT-SCT. In this ongoing phase II trial, data are available from 21 patients. After PAD induction, the ORR was 95%, including a 29% CR/nCR rate. Following HDT-SCT, the ORR remained the same but the CR/nCR rate increased to 57% [77]. These investigators also evaluated a modified PAD regimen, incorporating a lower dose of bortezomib, with the aim of reducing the incidence of peripheral neuropathy and other toxicities [78]. The ORR among 19 evaluable patients was 89%, including a 16% CR/nCR rate. Among 13 patients receiving HDT-SCT, the ORR post-transplant was 100%, with a 54% CR/nCR rate. These preliminary data suggest that PAD is an effective induction regimen prior to HDT-SCT. Although the numbers of patients enrolled were small, it appears that decreasing the dose of bortezomib improves the toxicity profile without significantly compromising the effectiveness of HDT-SCT in terms of the CR/nCR rate [78].

**Bortezomib plus Liposomal Doxorubicin**

The Cancer and Leukemia Group B (CALGB) is investigating the combination of bortezomib plus liposomal doxorubicin in a phase II clinical trial. Of 63 patients enrolled, response data are available for 29 patients who have completed study therapy; the ORR was 79%, with a 28% CR/nCR rate [79]. Key grade ≥3 hematologic toxicities included neutropenia, thrombocytopenia, lymphopenia, and anemia [79].

**Bortezomib plus Liposomal Doxorubicin and Dexamethasone**

The addition of liposomal doxorubicin to bortezomib and dexamethasone (VDD) is being investigated in a phase II study [80]. Among 28 evaluable patients the ORR was 89%, including a 32% CR/nCR rate [80]. Seventeen patients proceeded to HDT-SCT, resulting in an improved re-
sponse in 11 and increasing the ORR to 96% and the CR/nCR rate to 54% [80]. Grade ≥3 hematologic toxicities included thrombocytopenia and neutropenia [80].

**Bortezomib plus Thalidomide and Dexamethasone**

Thalidomide plus dexamethasone is used as a standard primary/induction regimen. Wang et al. [81] explored the addition of bortezomib to this regimen (VTD). The ORR with VTD was 87%, including a 16% CR rate. Responses occurred within one or two cycles in the majority of patients, eliminating the need for further treatment prior to HDT-SCT or maintenance therapy. Following HDT-SCT in 25 patients, the ORR in all 38 patients was 95%, including a 37% CR rate. The incidence of peripheral neuropathy did not suggest any additive neurotoxicity with thalidomide and bortezomib in patients who received up to three 4-week cycles of VTD. It should be noted that this regimen incorporated a relatively low dose of thalidomide (100–200 mg/day) and only 50% of the standard dose of dexamethasone, but treatment nevertheless produced a high ORR and CR rate.

**Bortezomib plus Thalidomide**

In addition to the VTD regimen, the steroid-free combination of bortezomib plus thalidomide has been investigated in a single-center phase II study. Among 27 evaluable patients, the ORR was 81%, including a 22% CR/nCR rate [82]. Baseline peripheral neuropathy was reported in 15% of patients, and all patients developed neuropathy by cycle 5 (grade 3 in 18%, no grade 4), assessed using the reduced Total Neuropathy Score; symptoms improved following dose reductions [82].

**Bortezomib plus Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide (VDT-PACE)**

Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE), a more intensive regimen, has shown efficacy in multiple myeloma [83, 84]. In a phase I study, Badros et al. [85] investigated the feasibility and toxicity profile of adding bortezomib to DT-PACE (VDT-PACE) prior to HDT-SCT. No dose-limiting toxicity was seen; neutropenic fever requiring hospitalization was observed in 25% of patients. The ORR was 83%, including a 17% CR/nCR rate, which improved to 92% and 58%, respectively, following HDT-SCT [85]. Early results of a large, ongoing phase II study using VDT-PACE as induction therapy prior to HDT-SCT show similarly high CR/nCR rates [86].

**Impact of Bortezomib Therapy on Stem Cell Mobilization and Collection**

It is an essential feature of all induction regimens used in patients eligible for HDT-SCT that they not impair stem cell mobilization and collection for transplant. Preclinical studies have demonstrated that bortezomib has no toxic effects on stem cells, megakaryocytes, or neutrophil precursors, and causes only transient and reversible thrombocytopenia and neutropenia [87, 88]. In the trials discussed above, assessment of stem cell collection and transplantation after frontline therapy with bortezomib indicated that adequate numbers of stem cells can be collected for both single [73, 74, 76, 77–80, 85, 86] and tandem [73, 74, 80, 85, 86] transplantations. Neutrophil and platelet engraftment were successful and as expected after HDT-SCT.

**Safety Profile of Bortezomib**

The side effects reported with the frontline use of bortezomib are predictable and manageable. Most commonly, these included fatigue, gastrointestinal events, and peripheral neuropathy; the most common adverse events graded 3 or higher were peripheral neuropathy, thrombocytopenia, neutropenia, and anemia. There were no unexpected toxicities observed, and the side effect profile was consistent with that seen in trials of bortezomib in the relapsed multiple myeloma setting [27]. Cumulative toxicity was not observed, even in elderly patients who received bortezomib for a prolonged exposure (median, 9 months) [67], again consistent with observations in the relapsed setting [89]. In studies of bortezomib-based combination regimens, toxicities were predictable and generally attributable either to bortezomib or the other agents used in the regimen.

**Peripheral Neuropathy**

For bortezomib, peripheral neuropathy is an important toxicity in the relapsed setting (35%–37% incidence, including a 9%–13% incidence of grades ≥3), though reversible in the majority of patients [90, 91]. As described above, neuropathy may be a more common feature of multiple myeloma itself than previously appreciated [62]. However, experience from bortezomib trials in the relapsed setting indicates that the presence of baseline neuropathy does not affect the overall incidence of peripheral neuropathy during bortezomib treatment [91]. A management guideline for bortezomib-induced peripheral neuropathy was developed in phase II trials [37, 38] and tested in the phase III APEX trial [27]. This advocated a stepwise strategy for dose reduction, through dose interruption, and if necessary, treatment cessation, enabling a greater number of patients to continue to receive bortezomib therapy. In one frontline study, dose modification
of single-agent bortezomib led to improvement or resolution in 75% of patients with peripheral neuropathy where follow-up data were available [62], reflecting observations previously made in the relapsed setting [90, 91]. With PAD therapy, peripheral neuropathy was the most frequently observed toxicity (reported in 48% of patients overall, grade 3 in 5%); importantly, all patients who experienced peripheral neuropathy improved or resolved to baseline [77]. The incidence of peripheral neuropathy appeared lower in the reduced-dose PAD study [78].

**Hematologic Toxicity**

The hematologic profile reported with bortezomib in the frontline setting reflected that seen in the relapsed setting [88, 92]. Bortezomib-associated thrombocytopenia is cyclical, recovering rapidly towards baseline during the rest period of each cycle [92]. Despite a higher incidence of thrombocytopenia, significant bleeding events (including those graded ≥3) were similar between the bortezomib and dexamethasone arms in the phase III APEX trial, reflecting the transient nature of thrombocytopenia seen with bortezomib [92]. Bortezomib may induce thrombocytopenia via a reversible effect on megakaryocytic platelet production (possibly by inhibiting platelet budding) rather than a direct cytotoxic effect [88]. Given the reversible nature, it has been suggested that platelet transfusion support rather than dose reduction may be warranted [88].

**Thromboembolism**

IMiDs are important agents in multiple myeloma therapy, and a common side effect of these agents is venous thromboembolism (VTE), notably when combined with dexamethasone or doxorubicin [63, 93–95]. When developing new IMiD-containing combination regimens, the possibility of an increased risk of VTE with the addition of other agents must be considered; this does not seem to be the case with the addition of bortezomib. Safety data from studies of regimens involving bortezomib in combination with thalidomide or lenalidomide do not appear to indicate an elevated thromboembolic risk with these combinations [40, 45, 48, 53, 55, 81, 82].

**Herpes Zoster**

Bortezomib treatment has been associated with an incidence of herpes zoster of 11%–13% in the relapsed setting [27, 37, 38], which has also been reported in studies in the frontline setting [67, 77, 82]. The causal mechanism is not yet fully understood; however, as reported in the study of VMP, the incidence of bortezomib-associated herpes zoster may be reduced with the use of prophylactic acyclovir [67].

**FUTURE DIRECTIONS**

Based on encouraging results from the phase II studies discussed above, several phase III trials have been initiated to help define the frontline role of bortezomib-based regi-

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Abbreviations: CR, complete response; DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; GMMG, German-speaking Myeloma Multicenter Group; HDT-SCT, high-dose melphalan therapy plus autologous SCT; HOVON, Stichting Hemato-Oncologie voor Volwassenen Nederland; IFM, Intergroupe Francophone du Myélome; MP, melphalan and prednisone; nCR, near CR; PAD, bortezomib, doxorubicin, and dexamethasone; SCT, stem cell transplant; VAD, vincristine, doxorubicin, and dexamethasone; VISTA, Velcade as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone; VMP, bortezomib, melphalan, and prednisone.
ments, including the IFM study comparing bortezomib plus dexamethasone with VAD [75]. These key studies (Table 3) will be pivotal in determining the effectiveness and utility of bortezomib-based regimens as primary induction therapy in multiple myeloma.

Extensive use of bortezomib in the frontline setting should not preclude its continued use in the relapsed setting. As discussed previously, preclinical studies have shown that bortezomib alone or in combination can overcome chemoresistance and sensitize multiple myeloma patients’ cells to other agents [24, 59, 60]. Experience in the relapsed setting has demonstrated that retreatment with bortezomib is feasible and that bortezomib-based combination regimens continue to demonstrate clinical efficacy in patients who have previously received bortezomib or other components of the combination [42, 43, 48, 49, 53, 56, 96–98]. These results suggest that bortezomib could remain an important option throughout the treatment algorithm.

In conclusion, bortezomib has demonstrated impressive efficacy in the frontline treatment of multiple myeloma. Bortezomib-based combinations have resulted in consistently high response rates and importantly, higher CR rates than with current standard frontline regimens. The optimal bortezomib-based combination has not been determined, but will depend in part on individual patient characteristics. Emerging results from clinical trials presented in this review suggest that bortezomib-based combination regimens will play an important role as primary therapy for multiple myeloma patients because of these high ORRs and CR rates. Reflecting the level of evidence in the frontline setting, bortezomib-based regimens have recently been added to the treatment protocol for newly diagnosed multiple myeloma patients in the updated National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, with VMP recommended for nontransplant candidates, and bortezomib plus dexamethasone and PAD recommended as induction for transplant candidates [4]. Although toxicity remains a concern, side effects have been predictable and manageable. The future of therapy for multiple myeloma is in highly active combination regimens, for which bortezomib will be an important component.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
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