Retrospective Comparison of Bortezomib-containing Regimens with Vincristine–Doxorubicin–Dexamethasone (VAD) as Induction Treatment Prior to Autologous Stem Cell Transplantation for Multiple Myeloma

Hyeon-Seok Eom1, Chang-Ki Min2, Byung-Sik Cho2, Seok Lee2, Jong-Wook Lee2, Woo-Sung Min2, Chun-Choo Kim2, Myungshin Kim3 and Yonggoo Kim3

1Hematology–Oncology Clinic, National Cancer Center, Goyang, 2Department of Hematology, The Catholic University of Korea and 3Department of Laboratory Medicine, The Catholic University of Medicine, Seoul, Korea

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Objective: Patients with multiple myeloma (MM) achieving high-quality responses, defined as a complete response (CR) and a very good partial response (VGPR) after transplant, benefit from high-dose therapy followed by autologous stem cell transplantation (ASCT). Induction pre-transplantation treatment with vincristine, doxorubicin and dexamethasone (VAD) is currently being replaced by new targeted agents with high anti-myeloma activity. The use of these novel agents may increase the CR+VGPR rate before ASCT, which may improve post-transplantation responses and survival.

Methods: We performed a retrospective analysis of 69 patients with MM who received bortezomib-containing regimens (n = 30) or VAD (n = 39) before collection of peripheral blood stem cells and ASCT.

Results: Objective response rate (at least a partial response) prior to ASCT was documented in 27 (90%) of 30 and 31 (81.6%) of evaluable 38 patients with bortezomib-containing regimens and VAD, respectively. The difference between the two groups was not significant (P = 0.494). However, the high-quality response rate with VGPR or more in the bortezomib group was significantly higher compared with the VAD group (66.7% vs. 34.2%, respectively, P = 0.006). The superiority of bortezomib-containing regimens in the high-quality response rate remained significant for only the newly diagnosed patients (n = 16, P = 0.008). The engraftment data as well as stem cell harvesting were comparable between the two groups. The major bortezomib-related toxicities were thrombocytopenias and peripheral neuropathies; toxicities of VAD were hematologic and infectious. After ASCT, the difference between the two groups did not reach the level of statistical significance with respect to progression-free survival and overall survival (P = 0.498 and 0.835, respectively).

Conclusions: The results of this retrospective comparison of bortezomib-containing regimens with the VAD as induction treatment prior to ASCT for MM provided a demonstration of the superiority of bortezomib therapy in terms of achieving a high-quality response. However, survivals following ASCT did not differ according to the induction regimens.

Key words: multiple myeloma – bortezomib – VAD – autologous stem cell transplantation – response – survival

INTRODUCTION

Autologous stem cell transplantation (ASCT) after high-dose chemotherapy is a part of the initial treatment plan for patients with multiple myeloma (MM). Although a large randomized trial has demonstrated superior response rates and
survival compared with conventional therapy, the disease eventually recurs and relapse remains the main reason for treatment failure after ASCT (1,2). It has been shown that the response to induction therapy in previously untreated MM patients is associated with prolonged survival in patients receiving ASCT (3). Therefore, the initial decrease in the myeloma burden may be the primary goal for patients who undergo ASCT and may translate into an improved survival benefit. Commonly accepted induction regimens include vincristine, doxorubicin and dexamethasone (VAD), dexamethasone alone, and thalidomide and dexamethasone (4).

Bortezomib (Velcade®, Millenium Pharmaceuticals Inc., Cambridge, MA, USA, and Johnson & Johnson Pharmaceuticals, Research and Development, L.L.C., Raritan, NJ, USA) is a first-in-class proteasome inhibitor that induces apoptosis and growth arrest and reverses chemoresistance in MM cells (5,6), and offers a novel approach to the treatment of MM in Phase II or III clinical trials producing rapid control (7–9). This novel agent is currently being evaluated in a number of clinical trials as part of front-line therapy in patients with MM. Results of three Phase II studies with bortezomib-based combinations in preparation for subsequent ASCT (10–12) and a randomized comparison of bortezomib with VAD were promising in terms of response rates and collection of adequate quantities of peripheral blood stem cells (PBSCs) (13). Together, the results from studies in the relapsed setting of bortezomib alone or in combination with other chemotherapeutic agents have led to the investigation of bortezomib in the front-line setting, both as a single agent and in combination.

Based on these data, bortezomib-containing regimens are currently accepted at many centers as a front-line treatment option for patients with symptomatic MM, particularly if it is planned to offer subsequent high-dose therapy with ASCT. However, few comparative studies of bortezomib with VAD, the reference treatment used thus far to reduce tumor cell mass prior to ASCT, have been reported (13). To address this unresolved issue, we performed a retrospective analysis of 69 patients who were treated with bortezomib-containing regimens (n = 30) or VAD (n = 39), in preparation for ASCT.

PATIENTS AND METHODS

PATIENTS AND DISEASE CHARACTERISTICS

Between October 1998 and June 2008, 69 patients with symptomatic MM from two institutions who consecutively received bortezomib-containing regimens (n = 30) or VAD (n = 39) before collection of PBSCs and ASCT were studied. We only included patients who received early transplantation, defined as ASCT within 12 months of the initial diagnosis of myeloma. The patients were required to have symptomatic MM diagnosed using standard criteria, and with measurable disease. All patients had a measurable level of monoclonal (M) protein. Measurable disease was defined as a monoclonal immunoglobulin (Ig) level on serum electrophoresis of at least 1 g/dl of IgG, 0.5 g/dl of IgA or 0.2 g/dl of IgM. Patients with light chain disease or non-secretory MM, who did not have M-protein at diagnosis, had measurable serum-free light chains (SFLCs) by the FreeLite test, as described elsewhere (14). The reference range for the SFLC concentrations was 3.3–19.4 mg/l for κ and 5.7–26.3 mg/l for λ.

TREATMENT REGIMENS

It was planned that bortezomib-based cytoreductive therapy and VAD would be administered for 3 and 4 months, respectively, in an attempt to reduce tumor cell mass prior to ASCT. The details on treatment regimens are available elsewhere (15,16). Briefly, bortezomib was given a median of 3 cycles (2–6) and consisted of either bortezomib alone (n = 7) or in combination with other chemotherapeutic agents (n = 23). Seven patients were treated with bortezomib alone (1.3 mg/m² intravenously, twice weekly for 2 weeks in a 21-day cycle) and 23 patients were treated with bortezomib (1.3 mg/m² intravenously, twice weekly for 2 weeks in a 21- or 28-day cycle) in combination with other chemotherapeutic agents, including oral dexamethasone (n = 7) or oral dexamethasone + doxorubicin (n = 16). Addition of the chemotherapeutic agents to bortezomib was determined based on the presence of co-morbidities, including diabetes mellitus, hypertension or other chronic illness. If the patient experienced febrile neutropenia, Grade 4 hematologic toxicity or any Grade 3 or higher non-hematologic toxicity considered to be related to bortezomib, bortezomib was withheld until toxicity returned to Grade ≤1 (excluding peripheral neuropathy). If the toxicity did not resolve within 2 weeks, bortezomib was discontinued. If the toxicity resolved, bortezomib was restarted at a dose reduced by 25% [1.3–1.0 mg/m² (bortezomib alone) and 1.0–0.7 mg/m² (bortezomib in combination)]. The combination treatment regimens were as follows: (i) bortezomib + dexamethasone; oral dexamethasone (20 mg) on the day and day after bortezomib administration for all cycles (21-day cycle); patients ≥60 years of age received a reduced dose (10 mg) and (ii) bortezomib + oral dexamethasone + doxorubicin (4.5 mg/m² on days 1–4 of each cycle). Pulsed dexamethasone combined with VAD was administered at a dose of 40 mg/day on days 1–4, 9–12 and 17–20 (odd cycles) and 40 mg/day for 4 days on even cycles, and repeatedly monthly. Vincristine and doxorubicin (by continuous infusion at the doses of 0.4 mg/day and 9 mg/m²/day, respectively, on days 1–4) were administered.

STEM CELL HARVEST PROCEDURE AND ASCT

In both groups, patients who proceeded to PBSC collection received high-dose cyclophosphamide (HD-CTX; 4 g/m²) and granulocyte colony-stimulating factor (10 μg/kg/day,
starting 5 days after HD-CTX infusion and continuing until the completion of PBSC collection. One-to-three harvests were performed after the CD34⁺ cell count in the blood (minimum target, 20/μL) was evaluated for each stem cell collection. The target yield was 5 × 10⁶ CD34⁺ cells/kg, which is the dose considered necessary to ensure safe engraftment in a double ASCT procedure. The patients were prepared for the stem cell transplantation with melphalan (200 mg/m²). The time-to-engraftment was defined as the time taken to achieve a neutrophil count of 0.5 × 10⁹ cells/L and a platelet count of 20 × 10⁹ cells/L.

EVALUATIONS

The criteria for defining a complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were previously reported by Bladé et al. (17); a very good partial response (VGPR) category (≥90% reduction of serum M-protein) was also included according to International Uniform Response Criteria (14). The primary endpoints of the study were to compare the overall response including high-quality response (≥VGPR) and survival between the bortezomib-based cytoreductive therapy and VAD as the induction treatment prior to ASCT. All responses had to be maintained for a minimum of 6 weeks. M-protein was measured by electrophoresis and immunofixation, when appropriate. Safety and toxicity were also secondary objectives of the study. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0).

STATISTICAL ANALYSIS

For the response category, the groups were compared using a χ² test (or Fisher’s exact test). Differences in the means of continuous measurements were tested by Student’s t-test and checked with the use of the Mann–Whitney U-test. The progression-free survival (PFS) was calculated from the day of ASCT until the time of relapse, disease progression or death, or the date the patient was last known to be in remission. Overall survival (OS) was measured from the day of ASCT to death due to any cause. The time-to-event analysis was performed using the Kaplan–Meier method. The differences in PFS and OS were compared using a log-rank test.

RESULTS

PATIENT CHARACTERISTICS

The median age was 53 years (range, 34–65 years) and 36 patients (52.2%) were males. All patients with VAD induction were previously untreated. In contrast, among the patients receiving bortezomib-based cytoreductive therapy, 16 (53.3%) and 14 (46.7%) patients were newly diagnosed and previously treated, respectively. Among the 14 previously treated patients, 10 patients had received only one prior treatment before bortezomib and 4 patients had received a third line or more. The demographics and disease characteristics among the groups are summarized in Table 1; the three groups were comparable with respect to major presenting variables known to potentially affect clinical outcome (all P values are > 0.05). When stratified according to the International Staging System, the bortezomib group included 6, 15 and 9 patients in Stages I, II and III, respectively, whereas the VAD group consisted of 10, 11 and 18 patients in Stages I, II and III, respectively. The median duration from diagnosis to ASCT was 243.5 days (range, 123–345 days) for patients treated with bortezomib-containing regimens and 223 days (range, 144–281 days) for patients treated with VAD.

Table 1. Baseline characteristics of all patients

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib-containing regimens (n = 30)</th>
<th>VAD (n = 39)</th>
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<tr>
<td></td>
<td>Newly diagnosed</td>
<td>Previously treated (n = 14)</td>
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<tr>
<td>Median age (year) (range)</td>
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<td>51 (34–62)</td>
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<tr>
<td>Sex, male/female</td>
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<td>9/5</td>
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<tr>
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<td>18/21</td>
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<td>Type of M-protein</td>
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<tr>
<td>IgG</td>
<td>7</td>
<td>19</td>
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<td>20</td>
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<td>17</td>
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<tr>
<td>Median hemoglobin (g/dl)</td>
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</tr>
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<td>Median β₂-microglobulin (mg/l)</td>
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<td>5.12</td>
</tr>
<tr>
<td>Median serum calcium (mg/dl)</td>
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<td>Median serum creatinine (mg/dl)</td>
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<td>Median serum albumin (g/dl)</td>
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<td>10/11/18</td>
</tr>
<tr>
<td>Median numbers of cycles (range)</td>
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</table>

VAD, vincristine, doxorubicin and dexamethasone.
RESPONSE TO THERAPY

Table 2 details the rates of response to the two induction regimens. An objective response rate (ORR; at least a PR) prior to ASCT was documented in 27 of 30 patients (90.0%) who were treated with a bortezomib-containing regimen. The ORR among patients who received VAD was 31 of evaluable 38 patients (81.6%). The difference between the two groups was not significant ($P = 0.494$). However, the high-quality response rate with VGPR or more in the bortezomib group was significantly higher compared with the VAD group (66.7% vs. 34.2%, respectively, $P = 0.006$). After ASCT, the difference between the two groups did not reach the level of statistical significance with respect to a high-quality response (71.4% vs. 63.5%, $P = 0.135$).

Analysis by the time of bortezomib treatment revealed that the percentages of patients with bortezomib-containing regimens who obtained the high-quality response were 75.0% and 57.1% in the newly diagnosed patients (vs. VAD, $P = 0.008$) and the previously treated patients (vs. VAD, $P = 0.203$), respectively. Both treatment groups had the same probability of attaining the ORR (93.8% and 85.7%, respectively) compared with the VAD group.

TOXICITY

Table 3 lists the common treatment-emergent adverse events in the bortezomib and VAD groups. The adverse event profile of the patients treated with bortezomib was similar to that reported previously (7–9). The most common toxicities with Grade 3 or more were peripheral neuropathies (30.0%), thrombocytopenias (36.7%) and neutropenias (16.7%). Other Grade 2 or more toxicities included constipation (30%), vomiting (10%), fatigue (10%), diarrhea (6.7%) and skin rashes (6.7%). Thrombocytopenia was cyclic, occurring during the administration of bortezomib, but recovering toward the baseline during the remaining period of each cycle. The major toxicities of VAD were hematologic, especially neutropenia; hematologic toxicity was severe (Grade 3 or more) in 35.9% of the patients. Infections of the upper respiratory tract occurred in 33.3% of the patients.

PBSC HARVESTING AND ENGRAFTMENT

Patients in each of the two groups received similar doses of HD-CTX. There was no significant difference between the two groups with respect to their characteristics at mobilization therapy with HD-CTX, except for the status of the disease and the size of the residual tumor mass. The median number of collected CD34$^+$ cells was $7.54 \times 10^6$ kg (1.93–40.5 kg) for patients treated with bortezomib and $8.32 \times 10^6$ kg (1.58–65.23 kg) for patients who received VAD ($P = 0.423$). In both treatment groups, the median number of aphereses performed to collect adequate cell yields was 2.

Complete hematopoietic engraftment was achieved in all patients who had received ASCT. Among patients treated with bortezomib, the median time until neutrophil and platelet regeneration was 10 days (range, 8–14 days) and 10 days (range, 0–17 days), respectively. Among patients treated with VAD, the median time until neutrophil and platelet regeneration was 10 days (range, 6–29 days) and 11 days (range, 0–34 days), respectively.

SURVIVAL

One patient in the bortezomib group died from severe mucositis and gastrointestinal bleeding 41 days after ASCT; one patient in the VAD group died of *Pneumocytis carinii*
pneumonia 101 days after ASCT. Only previously untreated patients were included for survival analysis. Figure 1A shows the PFS after the start day of the induction therapy according to the treatment groups. With a median duration of follow-up of 971.0 days (range, 270–3210 days), the median time to disease progression was 972 days (95% CI, 717.6–1226.4 days) in patients treated with VAD, whereas with a median duration of follow-up of 585.5 days (range, 215–794 days), the median time to disease progression in those treated with bortezomib did not reach the median value. There was no statistical significance with respect to PFS between the two groups ($P = 0.498$). Figure 1B shows the OS after ASCT according to the type of induction therapy in the newly diagnosed patients. With a median duration of follow-up of 1524 days (range, 270–3210 days), the median time to death was 2702 days (95% CI, 1486.3–3917.7 days) in patients treated with VAD, whereas with a median duration of follow-up of 620.5 days (range, 215–794 days), the median time to death in those treated with bortezomib did not reach the median value. There was no statistical significance with respect to OS between the two groups ($P = 0.835$).

**DISCUSSION**

High-dose therapy with ASCT is considered the standard care for patients with newly diagnosed MM who are younger than 65 years of age since it significantly prolongs the survival in comparison with standard-dose therapy (1,2). In patients who are candidates for ASCT, the treatment usually begins with three or four courses of induction chemotherapy, with the aim of reducing tumor cell mass prior to high-dose therapy without limiting stem cell mobilization or reducing the quality of the autograft. In such cases, VAD has been the standard treatment since it is not toxic to normal bone marrow stem cells and induces early responses, thus allowing patients to proceed to prompt stem cell mobilization.

The introduction of novel agents, such as bortezomib or thalidomide and its analogs, has provided an opportunity to improve induction therapy prior to ASCT. Thalidomide with dexamethasone has compared favorably to the standard VAD regimen as initial therapy in preparation for ASCT in terms of response and extent of tumor reduction (18). An important clinical question is the role of bortezomib-based cytoreductive therapy prior to ASCT. This study retrospectively evaluated the efficacy and safety of bortezomib-based cytoreductive therapy vs. VAD as an induction treatment before ASCT in patients with MM. There was a significant increase in the high-quality response (CR + VGPR) after bortezomib treatment in only the newly diagnosed patients when compared with VAD. The survival following ASCT did not differ according to the induction regimen. The more frequent toxicities included peripheral neuropathies with bortezomib and granulocytopenia with VAD.

Induction therapy is clearly essential to stabilize organ function and to improve performance status while the logistics of stem cell collection and transplantation are being organized. It is important that the primary induction regimen administered before transplantation is of low toxicity and does not impair the collection of PBSCs. In this light, several groups recently proposed the use of dexamethasone alone as a possible alternative to more toxic chemotherapies in preparation for subsequent high-dose therapy (19). With bortezomib alone or in combination with dexamethasone ± doxorubicin used in the present study, no irreversible toxicities were seen. Peripheral polyneuropathy and thrombocytopenia were the more frequent complications observed in patients with bortezomib treatment. The rates of peripheral neuropathy observed in the present study appeared to be higher compared with those reported in two other studies with primary bortezomib ± dexamethasone therapy, ranging from 31% to 48%, including a 5–16% incidence of ≥ Grade 3 (10,11). The inclusion of 14 (46.7%) previously treated patients in our study may have resulted in the increased incidence of neuropathies. It has been shown in a Korean study
(20) that Grade 2 or 3 polyneuropathies are more frequent in previously treated patients. It may be possible that the additional drugs to bortezomib in combination therapies contributed to more frequent peripheral neuropathies. A similar ease of mobilization was noted for a bortezomib induction regimen vs. VAD. Moreover, the successful and quick hematologic recovery and engraftment following transplantation make this treatment a safe and feasible alternative to current induction therapies.

The results of recently conducted Phase II clinical trials with bortezomib therapy alone and in combination with dexamethasone ± doxorubicin in previously untreated symptomatic disease showed a rate of response similar, or even superior, to that expected with conventional chemotherapy (10–12). Response rates seen in these studies ranged from 40% to 95% and provided a demonstration of marked activity for primary bortezomib-based combination regimens, but did not establish whether bortezomib therapy is or is not superior to the other induction chemotherapy. We found that the ORR (at least a PR) to the bortezomib-based regimen (90.0%) was not significantly higher than that observed with VAD (81.6%). Analysis the time of bortezomib therapy also showed that both groups (previously treated and untreated) had a similar ORR compared with the VAD group, respectively. In our patients, the frequency of response to VAD seemed to be higher than that originally reported by Alexanian et al. (21) and subsequently found by other groups using this regimen in preparation for ASCT (22,23). In agreement with our results, higher rates of response (up to 80%) were reported in other studies (24,25). Differences among studies with respect to baseline patient characteristics, treatment modalities (e.g. duration, continuous or bolus infusion of vincristine and doxorubicin, and total dose of dexamethasone) and criteria used to define response hamper a meaningful comparison of data and may easily explain the wide range of results reported thus far. With respect to the high-quality response, only the newly diagnosed patients benefited by bortezomib therapy, whereas the previously treated patients did not exhibit a superiority of bortezomib therapy compared with VAD, suggesting that bortezomib may be more efficacious in case of initial treatment or cross-resistant to conventional chemotherapeutic agents.

The achievement of a high-quality response, including CR or VGPR, is clinically relevant as it has been shown to be associated with better transplant outcomes and longer survival post-transplant (1,26). In the IFM90 trial, the depth of response was noted to be strongly correlated with OS. The 5-year survival was 72% for patients achieving CR/VGPR, 39% for a PR and 0% for <PR (2). A similar trend for improved survival was seen in the MRC VII and IFM94 trials (1,26). In this retrospective comparison, the increased rate of a high-quality response following bortezomib therapy did not translate into an improved response after ASCT. Among the previously untreated patients, the PFS and OS following ASCT were not significantly improved in the bortezomib group compared with the VAD group, even though the rate of a high-quality response before transplantation was significantly improved. The main reason why the survival following ASCT was not different between the two groups may be related to the similar depth of response after ASCT in spite of the inferior response after VAD, compared with bortezomib treatment. It has been shown that patients with primary refractory disease can benefit from ASCT to the same extent as those with responsive disease (27) because outcome may be dependent upon the final response after the transplant, independent of response to induction therapy. Moreover, the duration of median follow-up in the patients with bortezomib-containing regimens was radically different compared with the VAD group.

In conclusion, the introduction of novel agents, such as bortezomib, to induction therapy should improve the CR + VGPR rate with no stem cell toxicity prior to ASCT compared with VAD. Bortezomib-based cytoreductive therapy is a highly active addition to the armamentarium in the induction treatment of MM before ASCT and toxicities are predictable and manageable. However, assessment of survival data after ASCT did not show a better outcome with bortezomib in this retrospective study. More studies will be needed to determine whether bortezomib induction therapy is optimal according to transplant outcomes and adverse reactions prior to claiming it as a replacement for VAD as induction therapy prior to ASCT. Several Phase III trials have been initiated to help define the front-line role of bortezomib-based regimens, including the IFM study comparing bortezomib plus dexamethasone with VAD (13). The key study will be pivotal in determining the effectiveness and utility of bortezomib-based regimens as primary induction therapy in MM.

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Conflict of interest statement

None declared.

References


