Subcutaneous Administration of Bortezomib in Combination with Thalidomide and Dexamethasone for Treatment of Newly Diagnosed Multiple Myeloma Patients

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Objective. To investigate the efficacy and safety of the treatment of the newly diagnosed multiple myeloma (MM) patients with the therapy of subcutaneous (subQ) administration of bortezomib and dexamethasone plus thalidomide (VTD) regimen. Methods. A total of 60 newly diagnosed MM patients were analyzed. 30 patients received improved VTD regimen (improved VTD group) with the subQ injection of bortezomib and the other 30 patients received conventional VTD regimen (VTD group). The efficacy and safety of two groups were analyzed retrospectively. Results. The overall remission (OR) after eight cycles of treatment was 73.3% in the VTD group and 76.7% in the improved VTD group ($P > 0.05$). No significant differences in time to 1-year estimate of overall survival (72% versus 75%, $P = 0.848$) and progression-free survival (median 22 months versus 25 months; $P = 0.725$) between two groups. The main toxicities related to therapy were leukopenia, neutropenia, thrombocytopenia, asthenia, fatigue, and renal and urinary disorders. Grade 3 and higher adverse events were significantly less common in the improved VTD group (50%) than VTD group (80%, $P = 0.015$). Conclusions. The improved VTD regimen by changing bortezomib from intravenous administration to subcutaneous injection has noninferior efficacy to standard VTD regimen, with an improved safety profile and reduced adverse events.

1. Introduction

Bortezomib, the first potent therapeutic proteasome inhibitor, has been suggested as a standard care in patients with newly diagnosed and relapsed multiple myeloma (MM) [1]. Bortezomib is associated with high efficacy response rate when it is used as induction therapy before high-dose therapy (HDT) plus autologous stem cell transplantation (ASCT) [2, 3]. Intravenous injection is the standard route of bortezomib administration; the recommended dose and schedule of bortezomib is 1.3 mg/m$^2$ on days 1, 4, 8, and 11 of a 21-day cycle, for up to eight cycles, administered by 3–5-second intravenous (IV) bolus; this dose and schedule is active and well tolerated [4, 5]. However, IV administration requires repeated intravenous access or insertion of long-term central venous access devices and is usually associated with some serious adverse events [6].

Recently, two clinical trials have confirmed that subcutaneous (subQ) administration of bortezomib represents a good option to optimize the use of bortezomib for MM patients and results in a more convenient route that is at least as effective as the IV route [7, 8]. A phase I study conducted by French Francophone Myeloma Intergroup compared the pharmacokinetics and pharmacodynamics, safety and efficacy of IV, and subQ administration of bortezomib in patients with relapsed and/or refractory MM. The results demonstrated that subQ administration of bortezomib was possible because there were no differences in overall systemic availability and pharmacodynamic activity, toxicity profiles, and response rates in MM [7]. An international, multicenter,
A total of 60 patients with newly diagnosed MM were recruited in this retrospective analysis. 30 patients received VTD therapy and the other 30 patients received improved VTD therapy. Their demographic and baseline characteristics are summarized in Table 1. Among these patients, 35 were males and 25 were females; the median age was 56 years (range, 31 to 72 years). IgG MM was found in 26 patients, IgA in 16 patients, IgD in 5 patients, and light chain MM in 13 patients. 12 patients were stage I, 33 were stage II, and 15 were stage III. The baseline characteristics were similar in the two groups.

3.2. Efficacy. In both groups, patients received a median of six treatment cycles (range, four to eight). Overall remission (OR) after eight-cycle treatment was 73.3% in the VTD group (22 of 30 patients) and 76.7% in the improved VTD group (23 of 30 patients), including 4 patients (13.3%) getting complete remission (CR), 10 (33.3%) very good partial response (VGPR), and 8 (26.7%) partial remission (PR) in the VTD group and 3 patients (10%) getting CR, 11 (36.7%) VGPR, and 9 (30%) PR in the improved VTD group (Table 2). There was no statistical difference between the two groups (P > 0.05).

3.3. Prognosis. After a median follow-up of 24 (range, 3–36) months, we noted no significant difference in 1-year estimate of overall survival (72% versus 75%, P = 0.848) and progression-free survival (median 22 months, 95% CI 7.16–36.8, versus 25 months, 95% CI 9.08–36.1; P = 0.725) between VTD group and improved VTD group (Figure 1).

3.4. Safety. All patients experienced at least one adverse event. The main toxicities related to therapy in the two groups...
Table 1: Patient demographics and baseline characteristics (n = 60).

| Characteristic          | VTD group (n = 30) | Improved VTD group (n = 30) | P value |
|-------------------------|--------------------|-----------------------------|---------|
| Sex (male/female)       | 18/12              | 17/13                       | 0.793   |
| Median age (years, range)| 54 (31–67)        | 57 (34–72)                  | 0.712   |
| Myeloma type            |                    |                             |         |
| IgG                     | 12 (40%)           | 14 (46.7%)                  | 0.602   |
| IgA                     | 9 (30%)            | 7 (23.3%)                   | 0.559   |
| IgM                     | 2 (6.7%)           | 3 (10%)                     | 0.640   |
| Light chain             |                    |                             |         |
| ISS stage               |                    |                             |         |
| I                       | 6 (20%)            | 6 (20%)                     | 1.000   |
| II                      | 18 (60%)           | 15 (50%)                    | 0.436   |
| III                     | 6 (20%)            | 9 (30%)                     | 0.371   |
| Cytogenetics            |                    |                             |         |
| Diploid                 | 15 (50%)           | 13 (43.3%)                  | 0.605   |
| Hyperdiploid            | 6 (20%)            | 7 (23.3%)                   | 0.754   |
| Nonhyperdiploid         | 6 (20%)            | 8 (26.7%)                   | 0.542   |
| Hypodiploid             | 3 (10%)            | 2 (6.7%)                    | 0.640   |
| Interphase FISH         |                    |                             |         |
| t(4;14)                 | 15 (50%)           | 12 (40%)                    | 0.436   |
| del(17p13)              | 9 (30%)            | 14 (46.7%)                  | 0.184   |
| t(11;14)                | 6 (20%)            | 4 (13.3%)                   | 0.488   |
| Hemoglobin (g/L)        | 103 (71–144)       | 109 (73–159)                | 0.677   |
| Albumin (g/L)           | 37.5 (22–47)       | 36 (24–43)                  | 0.820   |
| β2 microglobulin (mg/L) | 3.9 (2.2–16.9)     | 4.3 (2.3–18.3)              | 0.754   |
| Platelets (<10^11/L)    | 243.4 (98.2–602.1) | 251.7 (79.3–533.2)         | 0.501   |
| Creatinine (mg/dL)      | 1.6 (0.4–3.7)      | 1.7 (0.2–4.1)               | 0.835   |

Table 2: Response to VTD regimen in each group.

| Response (n, %) | After 8 cycles |
|----------------|----------------|
|                | VTD group (n = 30) | Improved VTD group (n = 30) | P value |
| OR            | 22 (73.3%)        | 23 (76.7%)                  | 0.766   |
| CR            | 4 (13.3%)         | 3 (10%)                     | 0.688   |
| VGPR          | 10 (33.3%)        | 11 (36.7%)                  | 0.787   |
| PR            | 8 (26.7%)         | 9 (30%)                     | 0.774   |
| MR            | 4 (13.3%)         | 4 (13.3%)                   | 1.000   |
| SD            | 3 (10%)           | 3 (10%)                     | 1.000   |
| PD            | 1 (3.3%)          | 0                            | 0.313   |
| Not evaluable | 0                | 0                            | 1.000   |

OR (CR + VGPR + PR); overall response; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease; VTD: bortezomib and thalidomide plus dexamethasone.

Included leukopenia, neutropenia, thrombocytopenia, asthenia, fatigue, and peripheral sensory neuropathy (Table 3). Most adverse events were grades 1-2. Grade 3 and higher adverse events were reported in 24 of 30 (80%) patients in the VTD group and 15 of 30 (50%) in the improved VTD group ($\chi^2 = 5.943, P = 0.015$), with 8 (26.7%) and 3 (10%) discontinuing and 8 (26.7%) and 2 (6.7%) needing bortezomib dose reductions because of adverse events, respectively. Three of 30 (10%) patients in improved VTD group had one or more subcutaneous injection-site reaction reported, which resulted in a bortezomib dose modification in two (6.7%) patients (discontinuation or dose withholding). The most common reaction was injection-site erythema. No death related to therapy was reported in this study.

4. Discussion

In recent years, the outcome of MM patients has been significantly improved due to the discovery of novel antimyeloma agents together with a better knowledge of the pathophysiology of the disease. Among them, the proteasome inhibitor bortezomib (Velcade) represents an excellent drug that has quickly moved from the bench to the bedside and exhibits a powerful antimyeloma activity. Nowadays, bortezomib-based therapies are suggested as standards of care in patients with newly diagnosed and relapsed multiple myeloma [1]. In addition, abundant studies about the efficacy of bortezomib
as a single agent or in combination with other agents in relapsed and/or refractory as well as in newly diagnosed myeloma patients have emerged, and all data have contributed to confirming bortezomib as one of the key drugs of the backbone treatment of myeloma patients [9].

The triplet combination of bortezomib and thalidomide plus dexamethasone (VTD) regimen was one of the highly effective and well tolerated induction therapies for MM patients. In our study, the overall response rate was 73.3% with VTD regimen therapy, including 13.3% CR, 33.3% VGPR, and 26.7% PR in newly diagnosed MM patients. Previous phase 3 study by the Italian Group for Adult Hematologic Diseases (GIMEMA) compared VTD with TD as induction therapy in newly diagnosed patients [14]. The results showed that VTD produced significantly higher response rates than TD both after induction (94% overall
rate, including a 62% VGPR rate and a 32% CR/near-CR rate, versus 79% overall rate, including a 29% VGPR rate and a 12% CR/near-CR rate) and after transplantation (a 76% VGPR rate, including a 35% CR/near-CR rate, versus a 58% VGPR rate, including a 32% CR/near-CR rate). Combination of bortezomib with other immunomodulatory drugs and dexamethasone as induction therapy in newly diagnosed patients with MM also has been demonstrated in 2 studies of the comparison of bortezomib, the thalidomide analog lenalidomide, and dexamethasone, which produced a 100% overall response rate, including a 75% VGPR rate and a 40% CR/near-CR rate [15, 16]. These results and ours demonstrate that VTD regimen is highly active and well tolerated as induction therapy in patients with MM.

The primary goal of the retrospective study was to compare the subQ bortezomib-based VTD regimen and conventional VTD regimen as induction therapy for patients with MM. Subcutaneous administration of bortezomib has been shown to be noninferior to the standard intravenous route of delivery in patients with relapsed multiple myeloma and has an improved systemic safety profile [7, 8]. Recently, subQ bortezomib-based regimen has emerged and is considered as a promising alternative to intravenous administration, particularly in patients with poor venous access or at increased risk of side-effects [17–19]. In this study, the improved VTD regimen by changing bortezomib from intravenous administration to subcutaneous injection showed noninferior efficacy to standard VTD regimen. We recorded similarity between groups across all efficacy endpoints, including rates of OR and CR and very good PR after eight cycles. This finding accords with previous results showing similar response rates of MM patients treated with improved bortezomib, adriamycin, and dexamethasone (PAD, 61.1%) with the subQ injection of bortezomib and conventional PAD regimen (57.1%) [17]. We also found that there were no significant differences in time to 1-year estimate of overall survival (72% versus 75%, $P = 0.848$) and progression-free survival (median 22 months, 95% CI 7.16–36.8, versus 25 months, 95% CI 9.08–36.1; $P = 0.725$) between VTD group and improved VTD group. Taken together, this study provided further information that subQ administration of bortezomib is feasible and could contribute to optimizing the management of bortezomib in the treatment of myeloma patients.

We also provided important findings about the toxic effects of bortezomib in the subcutaneous group and intravenous group. The main toxicities related to therapy in the two groups were leukopenia, neutropenia, thrombocytopenia, asthenia, fatigue, and peripheral sensory neuropathy. Subcutaneous administration had an improved systemic safety profile compared with intravenous delivery, with lower rates of grade 3 or higher adverse events, and with fewer bortezomib dose reductions and discontinuations because of adverse events. Subcutaneous administration also had acceptable local tolerability; only 3 patients developed one or more subcutaneous injection-site reactions reported as an adverse event, as resulted in a bortezomib dose modification in two patients. All of these results confirmed that subQ bortezomib-based VTD regimen was not inferior to IV route, with even an improved safety profile.

In conclusion, VTD is highly active and well tolerated induction therapy for patients with MM. The improved VTD regimen by changing bortezomib from intravenous administration to subcutaneous injection has noninferior efficacy to standard VTD regimen and may become the front-line therapy for the newly diagnosed MM patients. Further studies in larger populations and a long follow-up are warranted to confirm the result.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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