Subcutaneous bortezomib incorporated into the bortezomib-thalidomide-dexamethasone regimen as part of front-line therapy in the context of autologous stem cell transplantation for multiple myeloma

High-dose therapy plus autologous stem cell transplantation (ASCT) is considered the standard of care for the front-line treatment of younger patients with multiple myeloma.[1] Response rates to induction therapy prior to ASCT have significantly increased through the use of novel agent-based combinations. Based on response rates, depth of response, and progression-free survival as surrogate markers for outcome, 3-drug combinations including at least bortezomib and dexamethasone are currently the standard of care prior to ASCT.[2] Three prospective studies have shown that the triplet combination consisting of bortezomib, thalidomide and dexamethasone (VTD) is superior to thalidomide-dexamethasone or bortezomib-dexamethasone alone.[3-5] Therefore, VTD has become one of the most commonly used regimens prior to ASCT, and 3-4 courses are recommended before proceeding to stem cell collection and ASCT. So far, in the era of novel agent-based induction therapy, consolidation therapy following ASCT is not a routine practice and is not generally recommended.[2] Nevertheless, VTD consolidation (2 cycles) following tandem ASCT was able to reduce the relapse rate and prolong PFS in the prospective trial conducted by the GIMEMA.[3,6] Moreover, in a recent retrospective analysis comparing VTD induction followed by single ASCT *versus* VTD induction, single ASCT and VTD consolidation (2 cycles), the IFM showed that the use of consolidation was associated with an improvement in response rates and PFS.[7] Therefore, the current IFM recommendations for the treatment of front-line MM in symptomatic patients eligible for high-dose therapy outside clinical trials are the following: VTD induction (4 cycles), ASCT prepared by melphalan 200 mg/m^2, followed by VTD consolidation (2 cycles).

Recently, the use of subcutaneous (SC) bortezomib was approved, based on the results of a prospective randomized study showing that, in the relapse setting, bortezomib SC was as effective as when the agent was administered intravenously (IV). Moreover, peripheral neuropathy (PN) of any grade, grade more than or equal to 2, and grade more than or equal to 3 was significantly less common with SC than IV administration.[8] Nevertheless, few data regarding the efficacy and the toxicity of SC bortezomib as part of front-line treatments are available.[9]

The aims of the current single-center study were to evaluate the response rates of the VTD regimen, with bortezomib administered subcutaneously, prior to and following a single ASCT step, and to confirm the reduction in the incidence of PN with SC bortezomib as part of front-line treatment.

From December 2011 to March 2013, 31 consecutive patients were prospectively studied. The treatment plan was: 4 cycles of VTD induction (SC bortezomib), stem cell collection following cyclophosphamide mobilization (3 g/m^2), ASCT prepared by melphalan 200 mg/m^2, 2 cycles of VTD consolidation (SC bortezomib). VTD cycles for induction and consolidation consisted of bortezomib 1 mg/m^2 on Days 1, 4, 8 and 11, thalidomide 100 mg/day administered orally, plus dexamethasone 40 mg Days 1-4 (all cycles) and Days 9-12 (cycles 1 and 2). The doses of VTD during the induction phase were identical to those previously reported in the IFM2007-02 trial.[4] Responses were assessed according to the IMWG criteria.[10]

Table 1. Patients' characteristics at diagnosis and responses to therapy.

	Number of patients (%)
Male/female	19/12
Median age	61 (range, 43-69)
IgG / IgA / light chains	17/9/5
ISS 1 / 2 / 3	4/17/10
t(4;14) / del17p	3/4
Response following induction	31
> VGPR	16 (51.6%)
> PR	27 (87.1%)
Stable disease	3 (9.7%)
Progression	1 (3.2%)
Response following consolidation	26
> VGPR	19 (73.1%)
> PR	26 (100%)
Stable disease	0
Progression	0

Patients' characteristics are listed in Table 1. On an intent-to-treat basis, following 4 cycles of VTD, the overall response rate (ORR) in 31 patients was 87%, including 52% very good partial responses (VGPR) or better (Table 1). Twenty-six patients (84%) completed the consolidation phase following ASCT. Five patients did not complete the whole procedure: 2 could not proceed to ASCT (1 progression, 1 infection), and 3 did not receive the 2 cycles of consolidation (1 toxic death from ASCT, 2 refusals). Overall, the median cumulative dose of bortezomib was 24 mg/m^2 (range 16-24) for a total planned dose of 24 mg/m^2. Following consolidation, the ORR was 100%, including 73.1% VGPR or better. Peripheral neuropathy rates are shown in Table 2. Following 4 cycles of VTD induction, the PN rate was 16% (all grades): including 13% grade 1 and 3% grade 2. No grade 3 or 4 PN were reported. After consolidation, the overall PN rate was 24%, including 12% grade 1 (3 patients), 8% grade 2 (2 patients) and 4% grade 3 (1 patient). Peripheral neuropathy was reversible in 2 patients (1 case of grade 1 and 1 case of grade 2).

Our study of 31 consecutive prospectively evaluated patients confirms the efficacy of the VTD regimen as part of induction therapy prior to ASCT. Of note, partial response (PR) and VGPR rates are identical to those observed in the IFM2007-02 trial, in which an equivalent population of patients was treated with 4 cycles of VTD using the same doses of bortezomib (in that trial administered IV), thalidomide and dexamethasone.[4] Consequently, the use of SC bortezomib in the present trial did not appear to affect the efficacy of the VTD combination. It is more difficult to compare the current results with those of the 2 other phase III trials that have incorporated VTD as part of induction prior to ASCT since the doses of IV bortezomib, of thalidomide, and the number of cycles were different.[3,5] On completion of consolidation therapy, the PR and VGPR rates seen in the present study compare favorably to those of the recent retrospective analysis of VTD induction, followed by single ASCT and VTD consolidation reported by the IFM for patients treated outside clinical trials, supporting the use of consolida-

Table 2. Peripheral neuropathy.

Peripheral neuropathy following induction	N = 31	%
Grade 1	4	13
Grade 2	1	3
Grade 3	0	0
Grade 4	0	0

Peripheral neuropathy following consolidation	N = 26	%
Grade 1	3	12
Grade 2	2	8
Grade 3	1	4
Grade 4	0	0

tion following ASCT.[7]

Our study also confirms that SC bortezomib is associated with a reduction in the incidence of PN. Following 4 cycles of induction, the PN rates were dramatically reduced as compared to those described in the IFM2007-02 trial outlined above.[4] In the IFM2007-02 study, the cumulative PN rate (all grades) was 56% *versus* only 16% in the current study, including 16% PN grade 2 or more in the earlier study *versus* 3% in the current trial.[4]

Overall, despite the relatively small number of patients enrolled in the present study, our results strongly suggest that SC bortezomib does not hamper the efficacy of the VTD combination when used as part of front-line ASCT. The reduction in PN associated with SC bortezomib supports the systematic use of this route of administration in the treatment of *de novo* MM patients. Furthermore, the reduction in the rates of neurotoxicity seen with SC administration also provides the possibility of using the full dose of bortezomib (1.3 mg/m^2) and a higher number of cycles as part of both induction and consolidation therapies.

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