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ORIGINAL ARTICLE

Safety and comfort of domestic bortezomib injection in real-life experience

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Abstract

Despite novel agents, multiple myeloma is still an incurable disease, especially for elderly and frail patients, who are difficult to manage for concomitant comorbidities as the therapeutic options are limited and the response to chemotherapy is often short. We report our evaluations upon safety and efficacy of domestic subcutaneous bortezomib in elderly and frail patients candidate to bortezomib-melphalan-prednisone (VMP) regimen. We confirmed that overall incidence of adverse events, including peripheral neuropathy, was low, and in no case required admission to emergency service, contributing to reduce the rate of therapy discontinuation. These results confirm the effectiveness and safety of subcutaneous bortezomib, in a real-life-experience, and define a new possibility of safe auto-administration in a comfortable domestic setting. We suggest that domestic treatment can significantly improve the quality of life of the patients, avoiding unnecessary transfer to the hospital without reducing treatment efficacy.

Keywords Multiple myeloma · Bortezomib · Supportive care · Safety · Subcutaneous

Introduction

The overall lifetime cancer risk is about 40% in Western countries, and it is well known that the combined incidence for all sites and types of cancer increases rapidly after age 60, especially in men [1].

Multiple myeloma (MM) is a hematological malignancy frequent in elderly and frail patients, with propensity to cause bone lesions, hypercalcemia, renal failure, and anemia [2, 3]. Bortezomib is the first-in-class proteasome inhibitor and when associated to immunomodulatory drugs (IMiDs) and dexamethasone increases the overall survival (OS) in MM [2, 4–8].

Despite novel agents, MM is still an incurable disease, especially for elderly and frail patients, who are difficult to manage for concomitant comorbidities as the therapeutic options are limited and the response to chemotherapy is often short lived. Unfortunately, the paucity of ultra-elderly patients (> 80 years old) included in clinical trials has made it difficult to define specific treatment strategies. Both in clinical trials and in daily clinical practice, elderly multiple myeloma patients have shown lesser benefit, due to less stringent use of proteasome inhibitors and immune-modulator reagents (IMiDs) lenalidomide and thalidomide, and early discontinuation of therapy for limited access to hospitals. Recent research in this patient population, however, has begun to reveal some important principles, such as the need for a comprehensive assessment as the basis for planning treatment to overcome the assumption that all or even most elderly patients are too frail to tolerate standard chemotherapy [9].

Data on the feasibility and efficacy of current standards of care are therefore lacking in frail patients. Age itself is far less important as a predictor of clinical outcome than is the older patient's physical, mental, emotional, and functional status. It now appears that, when given the same standard therapy, otherwise-healthy older patients can gain benefits comparable to those gained by younger patients. The high discontinuation rate and impaired quality of life could contribute to loss of efficacy in frail patients.

The current approach for elderly patients includes long-term treatment with at least nine cycles of induction chemotherapy, in order to achieve a sequential disease control

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approach [5, 9, 10]. Bortezomib has been shown safe, not requiring dosage adjustments in patients with renal impairment, skin or lung fibrosis, or mild hepatic impairment [11].

Recommended dose and schedule of bortezomib is 1–1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle, for up to eight cycles, administered by 3–5/s intra venous (IV) bolus. However, the once-weekly schedule significantly reduced the incidence of adverse events, including peripheral neuropathy (PN) and decreased the rate of discontinuation compared with the twice-weekly schedule, resulting in similar cumulative bortezomib doses, an important predictor of outcome [12–14].

Since IV administration may present some difficulties for patients with poor venous access and could limit dosage flexibility, the phase-3 MMY-3021 trial evaluated the efficacy of subcutaneous (SC) bortezomib administration leading to its approval by FDA in January 2012, by Health Canada in March 2012 and by CHMP-EMEA in June 2012. In general, safety data were similar for the SC and IV treatment groups, with a more tolerable profile for SC injection, due to a reduced incidence of neuralgia, peripheral neuropathy and thrombocytopenia, without affecting efficacy [15–18].

Millennium Pharmaceuticals recommended precaution in the vial reconstitution and administration, since the reconstituted concentration for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration for IV administration (1 mg/mL), even if preliminary data about PK and PD arising from MMY-3021 and CAN-1004 trials, showed that SC injection concentration (2.5 vs 1 mg/mL) had no appreciable effect [16]. Compared with IV administration, SC administration resulted in equivalent bortezomib plasma exposure, without affecting PK and PD parameters.

When bortezomib (3.5 mg in manufacturer's vial) is reconstituted with 1.4 mL NS, is physically and chemically stable for at least 1 week at 4 °C when stored in either the manufacturer's original glass vial or in a syringe and not exposed to light [19, 20].

Subcutaneous bortezomib administration has huge advantages to treat patients with poor venous accesses, and generally, it is convenient for both patients and physicians because it overcomes problems related to a prolonged intravenous infusion or the insertion of a long-term central venous access device. Moreover, overall incidence of peripheral neuropathy is lower with the subcutaneous administration in comparison with the intravenous route, reducing the possibility of a therapy discontinuation related to this adverse event [17].

In recent years, for some non histotoxic anti-cancer drugs, such as rituximab, trastuzumab, or cladribine, the subcutaneous route, as alternative to the intravenous one, has been successfully compared and the possibility of a self-administration modality for adequately informed patients or adult care-givers was also demonstrated [21, 22].

Based on this assumption, we designed an outpatients' program for domestic injection of SC bortezomib, associated to melphalan and prednisone (VMP) frail patients with difficulties to attain the hospital: evaluations upon the efficacy and safety are herein presented.

Material and methods

Patients selection

From January 2009 to June 2017, 63 frail patients requiring bortezomib for the treatment of MM, in association with orally administered prednisone and melphalan (VMP), performed SC injection of bortezomib at home for personal or logistic reasons. Initially, the drug was administered by qualified personnel; subsequently, the patient or an adult care-giver learned to inject it subcutaneously in the deltoid muscle area. Bortezomib was supplied in ready-to-use plastic syringes, where the drug was appropriately constituted in saline solution, under hood in sterile conditions by qualified personnel, few hours before delivering it to patients. Therefore, with an optimal storage stability temperature of 4 °C, the syringes were easily transported to patient in a refrigerated container, without affecting the chemical stability of the compound [19, 20].

Median age was 78 years old (range 59–87), with median Karnofsky PS 60% (range 40–90%).

Because of high dose steroids and bortezomib, the only exclusion criteria were psychiatric diseases or grade 2 or higher peripheral neuropathy. All patients were adequately informed in accordance with the Declaration of Helsinki.

Treatment

Patients received 4-week cycles of melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on days 1 to 4, bortezomib (1.0–1.3 mg/m^2) on days 1, 8, 15, and 22 (mean number of cycles 9, *r.* 3–12), according to a schedule adapted for frail patients [23–25].

The first cycle was usually administered at hospital to assess and confirm the safety of this route. Only 4 patients (6.3%) received also their first course at home, due to very poor clinical status.

Each cycle was proposed every 28 days for a total of 9 planned courses.

All patients received treatment with bisphosphonates every 4 weeks during the study. An antibiotic and antiviral prophylaxis was carried out with cotrimoxazole (800 mg twice a day, twice a week) and acyclovir 400 mg/die twice a day. Supportive therapy with erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF) was administered accordingly to ASH/ASCO guidelines [26], as reported in our previous experience in the same setting [27, 28].

Safety and efficacy assessment

Each patient's medical history was recorded on day 1 of each cycle. Physical examinations were conducted and blood was collected for hematology, renal and liver function tests 2 days before. Then, laboratory parameters were evaluated monthly or every 2 months, depending by clinical status of patient and disease stage.

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) criteria, version 4.0 [24].

Efficacy assessment was recorded after cycle 2 and every other cycle thereafter: myeloma protein evaluation by measuring serum and urine M component, beta-2 microglobulin, albumin and C-reactive protein (C-RP) and assessment of disease response according to the criteria of the International Myeloma Working Group [29]. Disease response was defined as complete remission (CR), very good partial remission (VGPR), partial remission (PR), stable disease (SD), progression disease (PD), or not valuable (NV).

Statistical analysis

Descriptive statistics were generated for analysis of results and p value < 0.05 was considered significant. Qualitative results were summarized in counts and percentages. Overall response rate (ORR) was defined as PR or better (CR+VGPR+PR). Progression free survival (PFS) was calculated from the time of inclusion until the date of progression, relapse, death or the date the patient was last known to be in remission and analyzed with Kaplan-Meier tests. Standard errors were calculated by the method of Greenwood, the 95% confidence intervals are computed as 1.96 times the standard error in each direction.

All calculations were performed using Graph Pad Prism version 5.00 for Windows, Graph Pad Software, San Diego California USA, www.graphpad.com.

Results

The median number of administered cycles was 7 (range 1–9), with a mean duration of treatment of 7.3 ± 0.7 months. Delivery of planned doses was as follows: 45/63 (71%) of patients received all doses of VMP, (18/63) 29% missed from 5 or more doses. Overall, 59 patients (93.6%) received all the doses of the cycles in a domestic setting, excepting 4 patients (6.3%), who received only the first administration at hospital, due to their frail clinical conditions, as mentioned above.

Treatment was interrupted after first two cycles in 18 patients for patient's will ($n = 3$), progressive disease ($n = 9$), and infection ($n = 6$). Drug reduction or delay administration was required only in 3 cases; thus, 45/63 of patients received all planned cycles at full dosage (Table 1).

The most common adverse events occurred during chemotherapy administration are reported in Table 2.

In about half of patients, the treatment was complicated by hematological toxicity, grade 3–4 in 37%. Thrombocytopenia was the most common hematologic toxicity, with grades 3–4 in 37%, without requiring platelet transfusion. Anemia grade 3–4 affected 19% of patients, and red blood cells were transfused in 13% of cycles, despite of EPO support. Neutropenia grade 4 affected 5% of patients, while G-CSF administration was needed to support 27 cycles (29%).

Among extra-hematological toxicities, nausea, vomiting, and diarrhea were mild, affecting 10% of cycles. Constipation was most commonly reported, especially at first 2 courses. Peripheral neurotoxicity was referred by two patients only.

Despite antibiotic and anti-viral prophylaxis was given according to internal guidelines [24, 26–28], Herpes Zoster reactivation occurred in three patients, managed successfully with standard antiviral treatment.

Three patients (3/63, 4.7%) were hospitalized for pneumonia (median days of hospitalization 6, with a range of 4–16) and received intravenous antibiotic treatment with resolution of infectious episodes. No patient died during treatment, and all of them re-started VMP with no further consequences. VMP did not affect the renal function.

Out of 45 patients who completed at least two cycles, the overall response rate (CR+VGPR+PR) was 72% (32 patients), including 32% (14 patients) negative-immunofixation complete remissions, 22% (10 patients) very good partial remissions and 18% (8 patients) partial remissions; 18% (8 patients) obtained a stable control of disease and only one patients progressed after five cycles.

After median follow up of 34.5 months (range 2.7–50 months), the median PFS was 12.3 months (Fig. 1), similar to what previously reported in similar settings of patients treated up-front with SC bortezomib in VMP regimen [17, 30].

Discussion

The combined strategy of care as domestic and outpatient setting for hematological diseases is still in debate. Given the costs of novel agents, the long-term treatment for frail patients with logistic limitation at home has been proposed as a suitable option for improving patient quality of life in a cost-saving approach for bortezomib-based regimens in MM. Data about efficacy and safety were similar to those observed in major clinical trials [2, 30–32] and other previous experience [5, 24, 25, 33–35]. In a recent report, Touati M. and colleagues showed the achievement of 16.5% of cost saving with the administration of two thirds of injection at home,

Table 1 Baseline characteristics of patients

Characteristics	Patients
Total patients	63
Sex	
Males, *n* (%)	29 (46)
Age, years	
Median, (range)	68 (59–87)
Paraproteins (isotype), *n* (%)	
Immunoglobulin G	39 (62%)
Immunoglobulin A	16 (25%)
Light chain only	8 (13%)
Stage ISS	
I	12 (19%)
II	22 (35%)
III	29 (46%)
Median Karnofsky PS (range)	60% (40–90)
Baseline hemoglobin, g/dL (range)	11.6 (8.7–14)
Baseline platelet count, · 10^9	161 (83–357)
Bone marrow infiltration > 50%, *n* (%)	41 (65%)
C-reactive protein, mg/l (range)	2.6 (1.7–26.2)
Lactate dehydrogenase, U/l (range)	173 (131–459)
Beta-2 microglobulin, mg/L	4.3 (0.9–16.4)
Serum albumin, g/dL (range)	3.4 (2.9–4.6)
Cytogenetics	
del13q	9 (14%)
t(4; 14)	5 (8%)
del 17p	8 (12%)
normal	29 (46%)
N.V.	12 (19%)

Table 2 Adverse events in the cohort of elderly and frail patients included in the study

No. events (%)	Total	Grade 3	Grade 4
Hematologic			
Trombocytopenia	31(50)	13(21)	10(16)
Anemia	28(45)	11(18)	1(1)
Neutropenia	32(51)	22(35)	3(5)
Gastrointestinal			
Nausea	29(46)	2(3)	1(1)
Diarrhea	30(48)	4(6)	0
Vomiting	19(30)	2(3)	0
PSN	32(51)	6(1)	1(1)
Infections			
Pneumonia	9(15)	4(6)	1(1)
Herpes Zoster	*n* [11]	2(3)	0

Total and grade 3/4 adverse events were reported in patients underwent to domestic treatment. PSN = peripheral sensory neuropathy

PSN peripheral sensory neuropathy

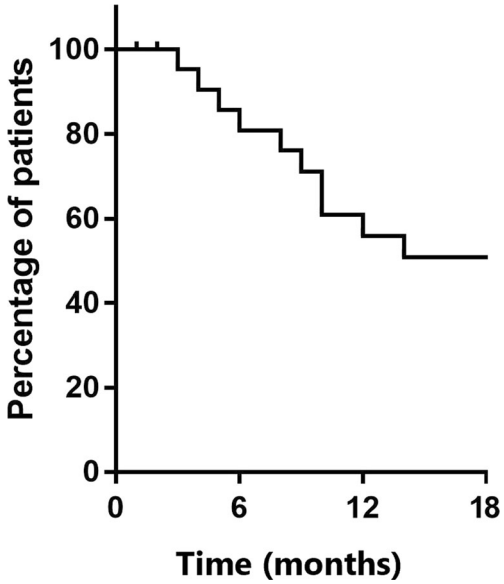

Fig. 1 Progression free survival in MM patients treated up-front with VMP regimen, using subcutaneous bortezomib, in a domestic setting

representing approximately 189 € saved per bortezomib injection in a retrospective study covering a geographical area comprising three Hematology units [36].

We reported our single-center experience in a similar setting of patients, confirming the effectiveness and safety of SC bortezomib, with the equal incidence of adverse events for outpatients' or domestic administration.

Based on final analysis of phase III MMY-3021 study which investigated the non-inferior efficacy with subcutaneous versus intravenous bortezomib associated to dexamethasone, best response rate was 52% in each arm, including 23 and 22% complete or near-complete responses with subcutaneous and intravenous bortezomib, respectively. Time to progression, progression-free survival and overall survival were comparable with subcutaneous versus intravenous bortezomib, with lower rate of peripheral neuropathy in SC bortezomib arm.

In real-life clinical practice, there is a common feeling to use only oral therapies for elderly and frail patients. Based on phase III VISTA trial, duration and quality of response upon VMP treatment improved global health status, pain, and appetite loss scores in elderly patients, in particular using the weekly schedule 1–8–15-22 [2], confirming the superiority of VMP on MP. Even if in absence of a formal prospective trial, a retrospective study showed that VMP was an independent predictor of longer PFS and OS. Indeed, in a control-case matched analysis, PFS and OS were prolonged in patients who received VMP in comparison with those treated with melphalan-prednisone-thalidomide (MPT) [37].

Based on our observations, obtained in a real-life experience, domestic treatment could significantly improve the quality of life of elderly patients, avoiding unnecessary transfer to

the hospital without reducing treatment efficacy. Multi-center studies are needed to address the schedule and feasibility in larger series to improve this approach in clinical practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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