Peer reviewed article

Daily practice use of Bortezomib in relapsed/refractory multiple myeloma

Safety/efficacy results of a compassionate use program in Switzerland

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Summary

Background: Several publications reported on the safety and efficacy of bortezomib, a novel first-in-class anti-cancer agent, in the treatment of relapsed/refractory multiple myeloma in controlled clinical trials. Complementary data on the experience with bortezomib in daily oncology practice are needed. We report on the use of bortezomib to treat patients with relapsed/refractory multiple myeloma in routine clinical practice.

Methods: Patients were treated at investigators' discretion within a Compassionate Use Program, allowing third-line or subsequent treatment. Post-hoc safety and efficacy analysis of patient records was performed using predefined data capture forms. Marker response was defined as a decrease in paraprotein level of at least 25% as compared to baseline.

Results: Eighty-eight patients entered the program involving 62 oncologists/ haematologists (62% institutional). Median patient age was 66 years [44–86], median time since diagnosis 4 years [0.5–14], median number of previous treatments 3 [2–6]. Marker response was observed in 61% of patients (17% CR/nCR). At the time of data collection, median 4.75 months [0.5–13] after last bortezomib injection, overall median response duration was 4.5 months [1.5–22], and response was ongoing in 45% of patients.

The most frequently reported adverse events were thrombocytopenia (34%), peripheral neuropathy (31%), diarrhoea (20%) and fatigue (19%). Among the cases of peripheral neuropathy, 68% were due to aggravation of a pre-existing condition and the remaining cases to onset under bortezomib. No cases of bortezomib-related haemorrhage were reported.

Conclusions: Our results in daily oncology practice confirm findings from clinical trials, demonstrating high response rates and predictable adverse events in patients with relapsed/refractory multiple myeloma treated with bortezomib.

Key words: bortezomib; multiple myeloma; daily oncology practice; peripheral neuropathy; thrombocytopenia

Introduction

Multiple myeloma is an incurable malignancy of differentiated plasma cells. The median length of survival after diagnosis is about three years [1] and approximately 25% of patients survive 5 years [2]. After a whole generation without any new agent against myeloma, the recent years have seen the approval of several new classes of drugs with anti-myeloma activity, including bortezomib (Velacade®).

Bortezomib is a potent, selective and reversible inhibitor of the proteasome [3]. This inhibition results in interferences within several critical intracellular signalling pathways controlling cell cycle [4], apoptosis [5], adhesion [6], transcription [7] and angiogenesis [8]. Moreover, bortezomib markedly enhances the sensitivity of myeloma cells to other chemotherapeutic agents, both *in vitro* [9] and *in vivo* [10].

Several clinical trials reported on the safety and anti-myeloma efficacy of bortezomib [11–13]. They led to the approval of this compound for third line therapy in many countries, including in Switzerland in January 2005. We took the opportunity of a one-year VELCADE® Compassionate Use Program, which ended at the time of product approval, to collect and analyse clinical data of the

The analysis was financially supported by Janssen-Cilag AG, Baar, Switzerland.

first myeloma patients treated with bortezomib in Switzerland. Aim of this analysis was to provide Swiss oncologists and haematologists with a first overview of the anti-myeloma activity and safety of bortezomib in routine oncology settings.

Methods

Patients and compassionate use program

"Compassionate Use" was defined according to the Swiss Agency for Therapeutic Products (Swissmedic) and the Program followed the regulatory framework issued by this Agency on this topic [14].

Patients enrolled in the Program had a relapsed/refractory myeloma after at least 2 and not more than 6 previous lines of treatment. Eligibility to participate in the Program involved further inclusion/exclusion criteria (table 1) essentially comparable to those of a published phase II registration study [11].

Although this was not a randomised trial, we defined an intention-to-treat (ITT) and a per-protocol (PP) population based on minimal exposure to treatment: ITT population included all patients having received at least one bortezomib injection, and a per-protocol (PP) population excluded patients who had received less than 8 bortezomib injections (<2 complete cycles) with irregular injections schedule. Data of the ITT population were solely analysed for safety and overall treatment response.

Treatment

While treatment modalities were basically at physician's discretion, the Program recommended 6 cycles of 1.3 mg/m^2 i.v. bortezomib on days 1, 4, 8 and 11, followed by a 10-days pause (21-days cycle). Addition of oral dexamethasone (20 mg the day of and the day after bortezomib administration) was recommended after 2 or 4 cycles in case of progressive or stable disease, respectively.

Physicians and Data Collection

Participating physicians were Swiss private or institutional oncologists/ haematologists. They received a data capture grid for each patient enrolled. Grids were filled out either by the physician or post hoc by a data manager. In this case, data were collected directly on the medical records, followed by an interview of the physician on treatment response and adverse event causality.

Efficacy/safety assessment

Response evaluation: Each physician was asked to evaluate his/her patient's best response to treatment according to generally accepted criteria, and in terms of progressive (PD), stable (SD) disease, minor (MR), partial (PR) complete/near complete (CR/nCR) response. Paraprotein level was documented when available. Since this data is heterogeneous in nature (M-protein, light chain), sample (serum, urine) and method of measurement (eg total immunoglobins or immunoelectrophoresis), each set of marker data was standardised toward its baseline level and results were expressed as percent reduction *vs* baseline marker value. This quantification was mainly used to evaluate cycles on which first and best responses occurred, as well as treatment response in case physician's evaluation was not available. Response was classified according to an EBMT-like scale, ie PD: increase in paraprotein level *vs* baseline value; SD: reduction by 0–25% *vs* baseline value; MR: reduction by 26–50%; PR: reduction by 51–94%; CR/nCR: reduction by ≥95%.

First response threshold was set on MR (paraprotein value ≤74% of baseline).

Adverse events (AEs) were either notified by the physician or registered on the medical records. Physicians were asked to evaluate if AE were unrelated, possibly related or probably related to bortezomib treatment. AEs reported as bortezomib-related were those considered by the physician to be probably or possibly related. Besides for thrombocytopenia and peripheral neuropathy, severity of AEs remained largely undocumented, since the present study was not a prospective clinical trial.

Table 1

Major eligibility criteria.

Multiple myeloma
At least 2 and not more than 6 previous lines of treatment
Relapsed or progressive disease
Karnofsky performance status ≥60%
Platelet count ≥30 × 10^9/L, with or without transfusion support
Haemoglobin ≥7.0 g/dL, with or without transfusion support
Absolute Neutrophil Count (ANC) ≥0.5 ×10^9/L
Serum calcium <14 mg/dL (3.5 mmol/L)
Aspartate Transaminase (AST): ≤2.5 × the upper limit of normal (ULN)
Alanine Transaminase (ALT): ≤2.5 × the ULN
Total bilirubin: ≤1.5 × the ULN
Creatinine clearance ≥20 mL/minute

Results

Physicians and sample population: From March 2004 to February 2005, 62 Swiss oncologists / haematologists (62% institutional) registered 91 multiple myeloma patients to enter the Program. From the 91 multiple myeloma patients 3 did not start the Program and data from 5 others were not available for this analysis. The intention-to-treat (ITT) population thus included 83 patients, 14 of which received less than 2 bortezomib cycles with irregular schedule, as revealed post hoc during data capture. This sub-population of 14 patients, all in an advanced progressive disease stage, received 3 bortezomib injections on average (range 1–7). Median time from the last bortezomib injection to date of death, available in 6/14 cases, was 18 days (range 7–23). Data of this sub-population were therefore analysed only for safety and overall treatment outcome. The remaining 69 patients constituted the per-protocol (PP) population, and, unless specified, all results below focus on this population.

Patient characteristics are summarised in table 2.

Treatment: Median number of bortezomib cycles completed at the time of data collection was 4 [2–19]; 70% of patients completed at least 4 cycles and 15% at least 8 cycles. The recommended start dose of 1.3 mg/m^2 was given to 94% patients, whereas 5% received 1.0–1.3 mg/m^2 and 2% less than 1.0 mg/m^2. At cycle 4, this ratio was 67, 23 and 10%, respectively; at cycle 6 the ratio was 48, 30 and 22%, respectively. Altogether 38% patients received corticosteroids in addition to bortezomib.

Treatment response: Of the 83 patients that started the Program (ITT population, at least one bortezomib injection), 51 (61%) had at least an MR. Of the 69 patients of the PP analysis (at least 2 cycles bortezomib), 74% responded (≥MR) to bortezomib (table 3), including 20% CR/nCR, 35% PR and 19% MR; 12% patients remained with stable disease (SD) and 15% had a progressive disease (PD).

Although proposed by the compassionate use program, the treating physicians have not measured paraprotein levels consequently. Paraprotein levels were available in 63 patients (altogether 272 measurements), and at least one measure per cycle was documented in only 33 patients (52%). We compared data from 40 patients, whose best response type was available from both physician's evaluation and paraprotein measure. Results indicate that the global proportion of CR/nCR, PR, MR, SD and PD do not differ significantly from one source to the other (chi^2 = 4.4, df = 5, ns).

Our data also show that among all paraprotein responses measured within the first cycle (n = 36), a decrease ≥2% *vs* baseline value was followed in 97% of cases by at least an SD and in 83% of cases by at least an MR. Factors such as sex, age, type of myeloma or number of previous therapies did not influence the response pattern to bortezomib, which, besides a slight age factor [11], corresponds to published results.

Time to response: In 38% of responders, first response (≥MR) occurred within the first cycle (figure 1). This ratio is probably underestimated, since in 17 out of 28 cases of first response occurring after the first cycle, this first response was also the first post-baseline paraprotein measure. At the third cycle, 96% of responders had started to respond. Best response was achieved within the first cycle by 11% of responders and by 69% within 3 cycles. In the other responders, continuation of treatment improved the quality of response.

Table 2

Patient and baseline characteristics. Means are expressed ± SD, median with [range].

Characteristics	Value
Age (yr)	65.2 ± 9.6
Male (%)	68.1
Time since myeloma diagnosis (yr)	4 [0.5–14]
Number of previous chemotherapies	3 [2–6]
Patients grafted at least once (%)	34.9
Patients with renal impairment (%)	50.0
Patients with peripheral neuropathy (%)	57.4
Patients with abnormal calcaemia (%)	40.4
Karnofsky performance status (score)	80 [60–100]
Leucocytes count (Giga/l)	5.0 ± 1.8
Platelet count (Giga/l)	207.8 ± 101.2
Haemoglobin concentration (g/l)	109.8 ± 17.3
Myeloma marker (% of total)	
Serum Ig	75.0
Urine light-chain	21.9
Non-secretory	3.1

Table 3

Overall response rate (% responders vs % non-responders) and best response achieved in the per-protocol population (at least two bortezomib cycles) and in the intention-to-treat population (at least one bortezomib injection)

Best Response Achieved	Per-Protocol (n = 69)			Intention-To-Treat (n = 83)		
	n	%	Responders vs Non-Resp	n	%	Responders vs Non-Resp
CR	6	8.7	73.9%	6	7.2	61.4%
nCR	8	11.6		8	9.6	
PR	24	34.8		24	28.9	
MR	13	18.8		13	15.7	
SD	8	11.6	26.1%	8	9.6	38.5%
PD	10	14.5		24	28.9	

Table 4

Documented adverse events (AEs). Related AEs were those rated by the physician as probably or possibly related to bortezomib treatment. AEs shaded in blue are those having occurred in ≥10% of patients (see text for percentages).

Adverse Event	Related	Unrelated	Unrated
Thrombocytopenia	27	1	0
Peripheral Neuropathy	25	1	3
Diarrhoea	16	5	1
Fatigue	15	8	5
Infection (a)	10[1]	19[2]	7
Nausea/vomiting	9	3	1
Dizziness/Hypotension	8	4	1
Constipation (b)	6[3]	6	1
Anorexia	3	2	0
Myalgia/Cramp	3	1	4
Bone pain	2	2	2
Exanthema	2	0	3
Fever	2	5	2
Headache	2	1	2
Nose bleeding	2	0	0
Sleep Disorder	2	0	1
Abdominal pain	1	1	0
Renal failure, acute	1	1	0
Agitation	1	0	0
Anaemia	2	3	1
Rash	1	2	2
Facial paralysis	1	0	0
Neutropenia	1	4	1
Oedema	1	3	0
Swallowing trouble	1	0	0
Tachycardia	1	0	0
Limb/back pain	0	8	4
Dyspnoea	0	5	0
Renal Failure, non-acute	0	4	0
Cough	0	2	1
Cardiac decompensation	0	1	0
Dehydratation	0	1	0
Flu-like Symptoms	0	1	1
Hypokalaemia	0	1	0
Incontinence	0	1	0
Paraplegia	0	1	0
Tinnitus	0	1	0
Visual Disorder	0	1	2
Anxiety/Depression	0	0	2
General discomfort	0	0	3
Hepatic failure	0	0	1
Total	145	99	51

[1] herpes n = 6 ; pneumonia n = 1
[2] herpes n = 3 ; pneumonia n = 4
[3] including 2 cases of ileus

Response duration: Eighteen weeks after treatment initiation, 76% of the responders were still responding (≥MR). At the time of data collection, median 4.75 months [0.5–13] after last bortezomib injection, overall median response duration was 4.5 months [1.5–22], and response was ongoing in 45% of PP patients (37% of ITT patients).

Median Karnofsky performance status increased from 80 [40–100] at baseline (data available for 52 out of 69 patients) to 90 [60–100] at cycle 2 and remained stable thereafter (median 90 [60–100] at cycle 6, data available for 14 out of 23 patients).

Safety analysis was performed on the data of 80 out of 83 ITT patients (data not available in three cases). Altogether, 295 AEs were documented (table 4), 244 received causality evaluation by the physician and 145 were considered bortezomib-related. Among the latter, the most frequent, occurring in ≥10% of patients in the AE cohort (n = 80), were thrombocytopenia (34%), peripheral neuropathy (31%, among which 68% consisted in aggravation of pre-existing neuropathy), diarrhoea (20%), fatigue (19%), infection (13%, among which 60% were herpes-related), nausea/vomiting (11%) and dizziness/hypotension (10%). Severity of thrombocytopenia could be documented in 19 out of 27 cases and was distributed as follows: 3 cases of grade 1, 6 of grade 2, 8 of grade 3 and 2 of grade 4 (CTC criteria). Both latter cases were already thrombocytopenic at baseline (grade 1 and grade 3). No cases of bortezomib-related haemorrhage were reported. Severity of peripheral neuropathy was evaluated in 16 out of 25 cases (64%) and was distributed as follows: 6 cases of grade 1, 4 of grade 2, 5 of grade 3 and 1 of grade 4.

Discussion

Bortezomib (Velcade®), a novel anti-cancer agent acting by proteasome inhibition, was approved in Switzerland in February 2005 for the third line treatment of relapsed/refractory multiple myeloma. We took the opportunity of a one-year Compassionate Use Program before approval to collect and analyse clinical data of the first myeloma patients treated with bortezomib in Switzerland in routine oncology settings.

The patients included in the Program were

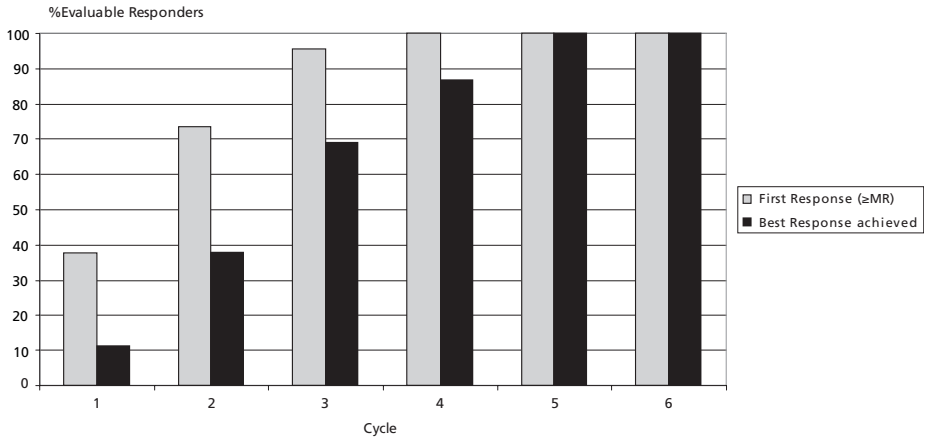

Figure 1

Cumulative percentage of first response (≥MR, blue) and best response (marker nadir level, red) achieved at each bortezomib cycle.

pretreated with 3 previous chemotherapy lines on average. An overall response rate (≥MR) of 61.4% was observed (ITT population). This rate was similar to the 62% of the CREST clinical trial [12], but higher then the 41% reported in SUMMIT [11]. This could be due to less heavily pre-treated patients in our analysis and in CREST (on average 3 previous treatments in both) compared with the SUMMIT trial (6 previous treatments on average). After a relatively short observation time (median 4.75 month) median overall response duration was 4.5 months and 45% of patients were still responding. Our results evoke a shorter response duration compared to SUMMIT (11.4 months) and CREST (9.5 or 13.7 months for patients treated with 1.0 or 1.3 mg/m^2, respectively). Shorter response duration was also observed in the VELCADE Compassionate Use Program in the Netherlands [15]. We assume that a less intensive treatment within the Compassionate Use Programs resulted in inferior treatment consolidation compared with the more strict treatment in prospective studies. In the presented study only 14.5% of patients received at least 8 cycles of bortezomib, whereas in SUMMIT and CREST these proportions were 39% and 27% respectively. In this context it is noteworthy that the recently published data from the APEX trial indicate that prolonged treatment can improve quality of response, while high quality response (100% M-protein reduction) appears to be associated with a longer duration of response [13].

The corpus of bortezomib clinical trials gives clues on ways to prolong the response to bortezomib: 1) by systematically adding dexamethasone in case of insufficient response [11], 2) by lowering the dose from 1.3 to 1.0 or 0.7 mg/m^2 in case of adverse event(s) rather than skipping an injection [12], 3) by prolonging the treatment of patients in remission to reach best response [13] and 4) by using bortezomib as early as second line treatment [16]. The latter option is now possible in Switzerland, since bortezomib was recently approved as second line therapy for relapsed or refractory myeloma.

Seven types of bortezomib-related AEs were reported in at least 10% of patients and accounted altogether for 76% of all drug-related AEs. The most frequent were thrombocytopenia and peripheral neuropathy (PN). Thrombocytopenia was not associated with severe complications (eg bleedings), often self-recovered during the rest period or was managed by dose reduction or platelet substitution. In the present survey we observed 10 cases with severe PN (4 grade 2, 5 grade 3, 1 grade 4) that is comparable with the findings in the main study by Richardson [13]. Clinical trials have shown that PN encountered during bortezomib therapy resolves or improves upon dose reduction or treatment interruption [17, 18]. Recommended algorithm to cope with bortezomib-related PN is the following: in case of PN grade 2, reduce dosage to 1.0 mg/m^2; in case of grade 3, withhold treatment until toxicity resolves, and then reinitiate at 0.7 mg/m^2 with schedule change to once a week. Importantly, these modifications do not appear to reduce time to progression [17]. Bortezomib should be discontinued in case of grade 4 PN. Altogether, bortezomib-related AEs were less frequently noticed in the Compassionate Use Program (mean 1.8 AE/patient) than in clinical trials (eg 4.2 AE/patient in SUMMIT), which might originate in differences in patient population, treatment schedule and settings.

We are aware of one publication on the use of thalidomide in daily practice within a compassionate use program for multiple myeloma [19]. In this program, thalidomide could be combined with dexamethasone and/or cyclophosphamide. The overall response rate (ORR = CR+PR+MR) was 62%. In the subgroup of patients undergoing thalidomide monotherapy the ORR was 50%, which is comparable to our results (ORR 61%). Due to cumulative neurotoxicity, patients tolerated only low doses of thalidomide (50–150 mg/day). We are not aware of data on the use of lenalidomide, a thalidomide-derivative, for the treatment of multiple myeloma in daily practice. The results from two Phase III clinical trials using lenalidomide [20] can hardly be compared with the results obtained with bortezomib in a large Phase III trial [16] for two main reasons: 1) lenalidomide was used until progressive disease, whereas bortezomib was used for a limited number of cycles, 2)

lenalidomide was used in combination with high-dose dexamethasone, 480 mg/cycle for 4 cycles and 160 mg/cycle until progression, whereas bortezomib was used as monotherapy. The lenalidomide/high-dose dexamethasone combination yielded a response rate (CR+PR) of nearly 60%, while bortezomib monotherapy achieved a response rate (CR+PR) of 43%. In the Phase III lenalidomide/high-dose dexamethasone and in the bortezomib trial median overall survival was close to 30 months. Reports indicate that the high efficacy of bortezomib monotherapy can be further enhanced by combining with other agents, such as dexamethasone [21, 22].

It should be noted that comparisons of cohorts from daily oncology practice *vs* those from clinical trials are difficult because of differences in settings, patient demographics and selection, as well as in study design (prospective *vs* retrospective). Because of these differences between clinical trials and daily practice, it is important to not only analyse the activity of an anticancer agent in clinical trials, but also investigate its effect in daily practice, as was done in the present project. From our analysis we conclude, that the use of bortezomib in daily clinical practice resulted in comparable encouraging high response rates as in reported studies with a predictable adverse event profile in patients with relapsed/refractory multiple myeloma.

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