Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma

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ABSTRACT

This phase I study compared pharmacokinetics and pharmacodynamics, and assessed safety and efficacy of intravenous and subcutaneous administration of bortezomib. Relapsed or refractory multiple myeloma patients were randomized to receive bortezomib by standard intravenous bolus (n=12) or subcutaneous injection (n=12) at the recommended dose and schedule (1.3 mg/m^2, days 1, 4, 8, 11; eight 21-day cycles). Plasma bortezomib concentration and percent 20S proteasome inhibition were measured at multiple time points on days 1 and 11, cycle 1. Systemic bortezomib exposure was similar between arms. As expected, mean maximum plasma concentration was lower and took longer to reach following subcutaneous administration. Overall 20S proteasome inhibition was similar between arms. Safety profile and response rate for the subcutaneous arm did not appear inferior to the intravenous arm, with good local tolerance of subcutaneous injection. Based on these exploratory findings, subcutaneous administration offers an alternative option to intravenous injection (ClinicalTrials.gov identifier: NCT00291538).

Key words: multiple myeloma, bortezomib, subcutaneous administration.

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Introduction

Outcomes for patients with multiple myeloma (MM) have improved significantly with the introduction of novel therapies,[1] including the proteasome inhibitor bortezomib. 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.[2,3] This dose and schedule is active and well-tolerated.[4-6] However, IV administration may present a treatment barrier for patients with poor venous access and could limit prescribing flexibility. In cynomolgus monkeys, bioavailability, exposure variability, and extent and duration of whole blood proteasome inhibition after subcutaneous (SC) bortezomib administration appeared comparable with IV administration.[7,8] SC administration demonstrated anti-tumor efficacy in human xenograft studies comparable with IV administration.[7] No unexpected toxicological findings were seen. This randomized phase I clinical trial compared pharmacokinetics and pharmacodynamics, and assessed safety and efficacy of IV and SC administration of bortezomib in patients with relapsed/refractory MM.

Design and Methods

Patients

Patients aged ≤ 75 years with symptomatic MM who had progressive disease after at least one prior therapy were eligible. Patients required measurable paraprotein in serum or urine; and adequate hematologic, renal, and hepatic function. Eligibility criteria and permitted concomitant medications are detailed in the *Online Supplementary Appendix*. Potent inducers/inhibitors of cytochrome P450 enzymes were not permitted during cycle 1; patients were not to use methylxanthine-containing products on days 1 and 11, cycle 1.

Study design

This open-label trial (ClinicalTrials.gov: NCT00291538) was conducted at three sites in France from January 26, 2006, to February 25, 2007. Patients were randomized (1:1), without stratification, to receive bortezomib (VELCADE®, Millennium Pharmaceuticals, Inc., and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) 1.3 mg/m^2, days 1, 4, 8, and 11, for up to eight 21-day cycles, by IV bolus (Arm A) or SC

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injection (Arm B). Final injection concentration in both study arms was 1 mg/mL. Anatomical areas of SC administration are summarized in the *Online Supplementary Appendix*.

Patients discontinued treatment due to progressive disease, insufficient efficacy, unacceptable toxicity, or serious protocol violation. Dose modifications were specified for unexpected pharmacokinetic observations or toxicity, as described in the *Online Supplementary Appendix*. Bortezomib-related neuropathic pain and/or peripheral sensory neuropathy were managed using established dose-modification guidelines.[9]

The primary objective was to characterize bortezomib pharmacokinetics, and secondary objectives were to characterize pharmacodynamics, safety, and efficacy, by IV and SC administration. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, and approved by Independent Ethics Committees of the participating centers. All patients provided written informed consent.

Pharmacokinetic/pharmacodynamic assessments

Blood samples for pharmacokinetic/pharmacodynamic analysis were collected on days 1 and 11, cycle 1: 30 min before bortezomib administration, and at 2, 5, 15, 30, and 60 min, and 2, 4, 6, 10, 24, 48, and 72 hours post-dosing. Pharmacodynamic analyses were performed using a whole-blood 20S proteasome specific activity inhibition assay.[10] Pharmacokinetic/pharmacodynamic analyses are summarized in the *Online Supplementary Appendix*.

Safety and efficacy assessments

Safety was monitored until 30 days after the last dose. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Assessment of cardiac safety was specified within secondary objectives. ECGs were recorded as described in the *Online Supplementary Appendix.*

Serum and 24-hour urine samples were collected at baseline, the end of each cycle, and four weeks after the last cycle. Investigators determined responses according to European Group for Blood and Marrow Transplantation criteria,[11] incorporating very good partial response.[12]

Statistical analysis

Sample-size determination and study power are described in the *Online Supplementary Appendix*. Specific pharmacokinetic and pharmacodynamic parameters were compared between arms using an analysis of variance (ANOVA) model to assess differences in least-squares means.

Results

Patients

Twenty four patients were enrolled, 12 in each arm. Baseline characteristics are summarized in the *Online Supplementary Appendix Table 1*. Median age was 61 years; median number of prior lines of therapy was two. Patient disposition is shown in the *Online Supplementary Appendix Figure 1*. Four patients in Arm A (IV) and 5 in Arm B (SC) completed treatment. Primary reasons for discontinuation were toxicity (6 and 3 patients in the IV and SC arms respectively), and disease progression (one and 3 patients). One patient in the SC arm discontinued due to a protocol violation (received day 8 and 11 doses, cycle 1, by IV infusion); he was evaluated for safety and efficacy within the SC arm.

Pharmacokinetics and pharmacodynamics

Ten patients in each arm were included in pharmacokinetic/pharmacodynamic analyses (*Online Supplementary Appendix Figure S1*). Pharmacokinetic parameters are summarized in Table 1; mean plasma concentration-time profiles on days 1 and 11 are shown in Figure 1A and 1B respectively. Systemic exposure of bortezomib was similar after IV and SC administration on days 1 and 11. Systemic exposures increased and clearance decreased after repeated administration (day 11 *vs.* day 1). Overall, exposure parameters in plasma were similar (relative bioavailability: F=82.5%, day 1; F=99.0%, day 11). Mean C_{max} was significantly higher with IV versus SC administration at both time points ($p<0.001$); median t_{max} was shorter but less than one hour in both arms. Inter-patient variability in C_{max} was high, with percent coefficient of variations of 163.3 and 50.5 in the IV and SC arms respectively.

Pharmacodynamic parameters are summarized in Table 1; mean percent inhibition–time profiles are shown in Figure 1C. Overall 20S proteasome inhibitory activity was comparable between arms at both time points, with no significant differences. Mean E_{max} was significantly higher with IV versus SC administration (day 1, $p=0.006$; day 11, $p=0.022$), and was observed within five minutes by IV administration versus approximately two hours after SC administration.

Safety

Treatment exposure and safety profiles are summarized in Table 2 and the *Online Supplementary Appendix Table S2*. Incidences and types of AEs appeared similar between arms. Only 2 patients, both in the IV arm, experienced grade 4 AEs; thrombocytopenia and osteosynthesis respectively. No deaths during treatment were reported. Within the SC arm, an injection site reaction was reported following 51% of administrations. No severe local reactions, such as ulceration or necrosis, were reported. The most common reaction was injection-site erythema, reported in 11 patients. Local reactions did not require treatment with local or systemic therapy. ECGs showed that QTc intervals (Bazett and Fredericia formulae) were similar between arms at baseline; all patients in the IV arm had QTcB and QTcF intervals ≤450 msec, versus 9 and 11 patients respectively in the SC arm. Minimal changes were reported post-dosing for both arms. No ECGs from any patient had QTc interval increases >30 msec; negative mean changes from baseline were noted at nearly every time point in both arms.

Efficacy

Best responses are summarized in Table 2. Overall, 50% of patients achieved partial response or better. Response rate did not appear inferior with SC versus IV administration; the response rates between arms appeared similar, however this study was not designed to determine efficacy differences.

Results and Discussion

This phase I study represents the first clinical investigation of the SC route of administration of bortezomib. Our results indicate that SC administration is comparable with the established IV route, with no differences in overall systemic availability and pharmacodynamic activity, similar toxicity profiles, and similar response rates in MM. Our pharmacokinetic data clearly demonstrated no significant differences in systemic availability between SC and IV administration on days 1 and 11, cycle 1. Mean plasma C_{max} values were significantly lower with SC administration; this was expected, given the time required for subcutaneously administered drugs to be absorbed. Mean volume of distribution was similarly high in both arms, confirming that bortezomib distributes extensively into peripheral tissues.[2] Our data on maximum plasma concentration and systemic availability following IV administration demonstrated substantial inter-patient variability; mean values appeared somewhat higher than reported in a previous pharmacokinetic/pharmacodynamic study of two bortezomib doses given intravenously to a similar patient population.[13] This may have been due to our use of two minutes as the first sampling time point, versus five minutes in the previous study,[13] and our consequent identification of an earlier and higher C_{max}. Our pharmacodynamic analyses demonstrated no significant differences in overall 20S proteasome inhibition between IV and SC administration. Reflecting pharmacokinetic profiles, mean E_{max} was significantly lower and Tmax longer following SC administration. These findings indicate there is a less-pronounced initial *spike* in proteasome inhibition by SC administration, although cumulative pharmacodynamic activity is comparable with IV administration. Overall, the safety profile for SC administration appeared similar to that for IV administration reported in comparable patient populations,[4,6,13] with no new systemic AEs and no evidence of immune-mediated reactions with SC administration; the small sample size precludes any definitive statement regarding differences in side effects. Local tolerance of SC infusion was satisfactory, except for limited, reversible erythema that never

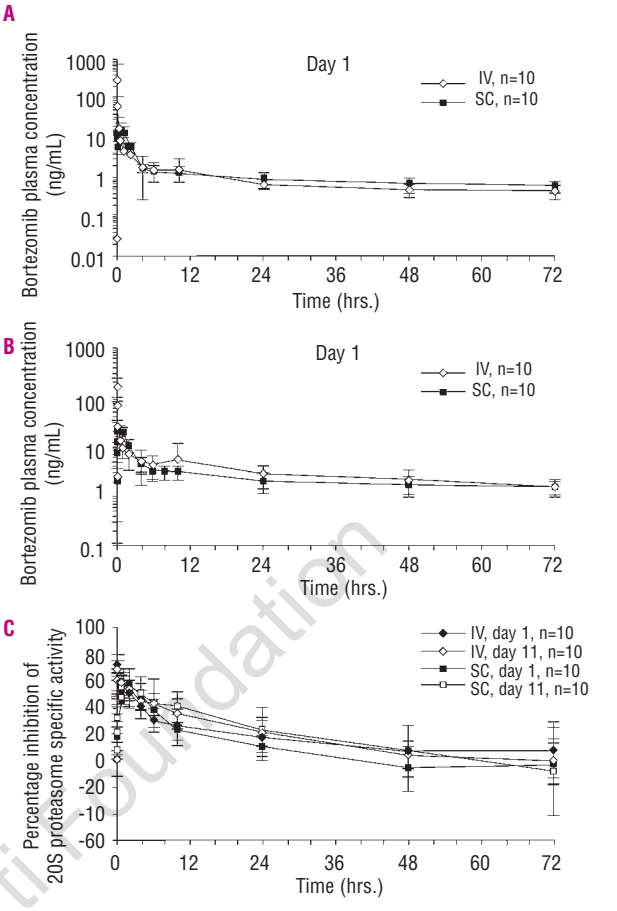

Figure 1. **Pharmacokinetic and pharmacodynamic profiles of bortezomib following intravenous or subcutaneous administration. Mean plasma concentration–time profile on (A) day 1 and (B) day 11; (C) mean whole-blood 20S proteasome specific activity (SpA) inhibition–time profile on days 1 and 11.**

Table 1. **Mean (SD) plasma pharmacokinetic parameters of bortezomib and whole-blood 20S proteasome inhibition after intravenous or subcutaneous administration on day 1 and day 11.**

	Day 1		*Day 11*	
	Arm A – IV (n=10)	*Arm B – SC (n=10)*	*Arm A – IV (n=10)*	*Arm B – SC (n=10)*
PK parameters				
tmax, h*	0.03 (0.03–0.05)	0.53 (0.30–1.02)	0.03 (0.03–0.50)	0.50 (0.25–1.00)
C_{max}, ng/mL	286 (466)	16.5 (8.35)†	162 (79.9)	22.5 (5.36)†
AUC_{∞}, ng.h/mL	183 (158)	151 (53.5)‡	409 (187)	405 (138)¶
AUC_{last}, ng.h/mL	104 (99.0)	92.1 (17.8)#	241 (82.0)	195 (51.2)§
CL, L/h	17.9 (8.22)	–	6.60 (3.15)	–
CL/F, L/h	–	16.6 (5.82)	–	6.22 (2.41)
Vd, L	1636 (850)	–	538 (194)	–
Vd/F, L	–	1330 (578)	–	765 (322)
Vd_{ss}, L	1370 (757)	–	463 (180)	–
$t_{1/2}$, h	98.1 (145.0)	65.7 (46.5)	66.7 (40.7)	95.2 (52.2)
PD parameters				
t_{max}, h*	0.03 (0.03–0.97)	2.02 (0.57–4.00)	0.05 (0.03–0.50)	2.00 (1.00–4.00)
E_{max}, %	71.3 (7.28)	57.7 (11.8)††	68.8 (6.49)	57.0 (12.8)‡‡
AUElast,%.h	1297 (734)	822 (542)¶¶	1283 (595)	1619 (804)##

**Median (range) data presented; †p<0.001, ‡p=0.979, ¶p=0.865, #p=0.738, §p=0.187, ††p=0.006, ‡‡p=0.022, ¶¶p=0.113, ##p=0.640 for comparisons with IV administration, ANOVA method. AUC_{∞}: area under the plasma concentration-time curve from time zero to infinite time; AUClast, area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; AUElast, area under the proteasome inhibition-time curve from time zero to the last sampling time point; CL, total clearance of drug after IV administration; CL/F, total clearance of drug after extravascular administration, corrected for absolute bioavailability; Cmax, maximum plasma concentration; Emax, observed maximum percent inhibition of 20S proteasome activity, taken directly from the inhibition-time profile; IV, intravenous; PD: pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; tmax, time to reach Cmax (PK) or Emax (PD); Vd, apparent volume of distribution; Vd/F, apparent volume of distribution after extravascular administration, corrected for absolute bioavailability; t1/2, elimination half-life.*

Table 2. Overview of treatment exposure, adverse events, and best response to bortezomib by route of administration.

	Arm A–IV administration (n=12)	*Arm B–SC administration (n=12)*
Treatment exposure		
Median n. treatment cycles,	6	6
Median total dose, mg/m^2	28.55	24.25
AE, n (%)		
Any AE	12 (100)	11 (92)
Any grade ≥3 AE	9 (75)	7 (58)
Any serious AE	5 (42)	1 (8)
Any AE causing discontinuation	6 (50)	3 (25)
Any AE requiring dose reduction	4 (33)	7 (58)
Grade 3/4 AEs*		
Neutropenia	6 (50)	2 (17)
Thrombocytopenia	3 (25)	3 (25)
Neuropathy	2 (17)	2 (17)
Anemia	1 (8)	1 (8)
Leukopenia	1 (8)	1 (8)
Response, n (%)		
Overall response rate (CR+VGPR+PR)	5 (42)	7 (58)
CR	1 (8)	1 (8)
VGPR	3 (25)	2 (17)
PR	1 (8)	4 (33)
MR	4 (33)	1 (8)
NC	3 (25)	1 (8)
PD	0	1 (8)
Not evaluable	0	2 (17)

**Reported in more than one patient. AEs of any grade reported in ≥25% of patients overall are listed in Supplementary Appendix Table 2. AE: adverse event; CR: complete response; IV: intravenous; MR: minimal response; NC: no change; PD: progressive disease; PR: partial response; SC: subcutaneous.*

required local or systemic therapy. Neither IV nor SC administration was associated with any clinically significant QTc prolongation. Response rate did not appear inferior in the SC arm; overall response rate was similar to that reported in a phase 3 study of IV bortezomib 1.3 mg/m^2.[14]

In conclusion, SC administration of bortezomib seems comparable with established IV administration. Further studies in larger populations are warranted to confirm preliminary toxicity and efficacy data; an international study is planned to commence in 2008. SC administration could represent an alternative to IV injection.

Authorship and Disclosures

PM and JLH were involved in conception and design of the study; PM, VC, CH, XL, and JLH participated in data collection. PM, HvdV, MA, and JLH were involved in data analysis and interpretation. PM, HvdV, MA, and JLH wrote the first draft of the manuscript, and all co-authors listed participated in the critical review of the manuscript for scientific content and approved the final manuscript. Two of the authors (HvdV and MA) are employees of Johnson & Johnson Pharmaceutical Research & Development, the study sponsor. Three authors (PM, CH and JLH) have received honoraria from Johnson & Johnson Pharmaceutical Research & Development. No other authors have any conflicts of interest to declare.

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