Abstract. This review presents the clinical pharmacokinetics of bortezomib. Aspects regarding metabolism, pharmacodynamics and drug interactions are also discussed.

Bortezomib (formerly known as PS-341) is an anticancer agent currently approved as second line in the treatment of multiple myeloma and recently (December 2006 in the United States) in the treatment of mantle cell lymphoma, an aggressive form of non hodgkin lymphoma. This drug was initially developed for use in the areas of cachexia and inflammation until the establishment of its antitumoral activity in 1997 (1). Its clinical development was rapid and its first approval (May 2003 in the United States) was based upon the results of a phase II trial showing a promising response rate (28%, including some complete responses) in 193 highly pretreated and refractory patients with myeloma (2). Bortezomib has already generated a lot of literature particularly regarding its complex and original mechanism of action (see 3-5 for recent reviews). However, less attention has been devoted to the disposition of this new drug. The goal of this paper is to review what is known about the clinical pharmacokinetics of bortezomib based on the published literature.

Pharmacological Properties

Bortezomib (molecular weight: 384.24) is a dipeptide derivative of boronic acid that acts as a reversible enzyme inhibitor. Bortezomib interferes with the proteasome, a multi enzyme protease complex present in the cytoplasm and nucleus of cells and involved in the majority of protein degradation. Bortezomib reversibly inhibits the catalytic activity (more precisely the chymotryptic-like activity) located in the 20S subunit (also called the 20S proteasome) with a inhibition constant K_i of 0.62 nM (230 ng/L) (6). Blocking the degradation of key proteins in cancer cells such as the inhibitor (I\(\kappa\))-B of the transcription nuclear factor kappa B (NF-\(\kappa\)B) leads to apoptosis (5). Antitumor effects of bortezomib alone or in combination also occur independently of NF-\(\kappa\)B inhibition (5, 7). Interestingly, in fact a prerequisite to its clinical development, quiescent normal cells are relatively indifferent to proteasome inhibition (4). The reason is unclear but could be partly related to the differences in the proliferative rates and in the protein turnover (4).

Preclinical studies have demonstrated cytotoxicity against various cell lines and tumor regression in xenograft models (8, 9).

Regarding myeloma (the major indication), antiangiogenic effects on endothelial cells from bone marrow of patients have also been shown (10). Furthermore, myeloma is clinically characterized by bone destruction resulting from activation of osteoclasts and impaired function of osteoblasts (11). Proteasome inhibition in osteoblasts increases their number in cultures and promotes bone formation in mice (12). Enhanced osteoblast activity based on serum markers (bone-specific alkaline phosphatase, osteocalcin) was reported in 25 patients with myeloma treated by bortezomib (13). Markers did not change in a control group treated with other drugs. This suggests that besides antitumoral activity (myeloma cells), bortezomib might affect bone formation by interacting with osteoblasts (13).

Clinical development in the treatment of myeloma was mostly based on the complete response obtained in a patient with advanced disease during a phase I trial (14). Bortezomib has also been tested alone or in combination in numerous types of solid tumors and hematological malignancies. Bortezomib represents the first, and currently the sole, licenced member of this class of anticancer drugs called proteasome inhibitors.
Drug Formulation and Administration

Bortezomib is administered intravenously and is formulated with mannitol as a lyophilized powder. Each vial contains 3.5 mg of bortezomib. The recommended dosage for adult patients with pretreated myeloma or mantle cell lymphoma is 1.3 mg/m² given as a bolus injection twice weekly, for 2 weeks with a 1 week rest in a 21-day cycle, as a monotherapy. As seen below, there are no published pharmacological data to support body surface area-based dosing. The treatment includes 6 to 8 courses.

Analytical Methodology

To date, no validated assay has been published as a full paper. Analytical difficulties have been encountered in the characterization of pharmacokinetics in animals. Plasma concentrations related to the elimination phase were below the limit of detection probably due to the low dose administered in association with a rapid distribution. Tissue distribution data have been obtained in rats by quantitative whole-body autoradiography (8). However, the manufacturer has developed a liquid chromatographic method with tandem mass spectrometry detection for the quantitation of bortezomib in human plasma (15). The lower limit of quantitation (LLOQ) is 0.5 ng/mL for the parent drug allowing the determination of plasma concentrations up to 24 h after administration. This technique has been used to determine the pharmacokinetics in patients with prostate cancer (15). A liquid chromatographic method with ultraviolet detection has also been reported for the determination of bortezomib in pharmaceutical (i.e., non biological) samples with a limit of detection of 300 ng/mL (16), well above the peak concentration in plasma (15). An alternative approach to evaluate bortezomib disposition has been to determine its biological activity by measuring the inhibition of the 20S proteasome in white blood cells (17).

Pharmacokinetic Properties

The clinical pharmacokinetics of bortezomib have been initially investigated in patients with solid tumors (15, 18). Bortezomib disposition has been examined in patients with myeloma very recently (19).

Absorption. In the early phases of its development, bortezomib was judged orally bioavailable (20) and was tested via the oral route in mice (8). The oral administration has not been evaluated further and no data have been published regarding absorption parameters.

Distribution. The distribution of bortezomib in humans has not been reported. Rat experiments using the radiolabeled drug revealed high levels of radioactivity in the gastrointestinal tract 24 h after injection (8). No radioactivity was detected in the brain. In line with a possible limitation of penetration in human brain tissue, Mele et al. (21) reported the absence of activity of bortezomib in a patient with cerebral involvement of myeloma.

Metabolism. Contrasting with the paucity of plasma pharmacokinetic data, the metabolic profile of bortezomib is well established, both in vitro and in vivo. Thirteen circulating metabolites have been identified by mass spectrometry in plasma of 8 patients who received a single injection of bortezomib (22). The major metabolites called M1 and M2 are carbamidamido diastereomers resulting from oxidative deboronation. Additional minor metabolites were also observed mostly produced from M1 and M2. All characterized metabolites are without the boron atom and are considered to be inactive (22). However, the overall contribution of metabolism to bortezomib elimination remains unknown in humans.

In vitro experiments on human liver microsomes showed the same pathway of biotransformation (oxidative deboronation) (22). Moreover, formation of M1 and M2 were catalyzed by multiple cytochrome P450 (CYP) isoenzymes such CYP3A4, CYP1A2, CYP2D6, CYP2C9 and CYP2C19 (21). More precisely, CYP3A4 (38.4%), CYP2C19 (30.1%) and CYP1A2 (10.5%) to a lesser extent were shown to be the major contributors to in vitro the disappearance of bortezomib at 2 µM or 768 µg/L (23).

Excretion. The excretion pathways of bortezomib in humans remain unpublished.

Pharmacokinetic Parameters. Plasma pharmacokinetics were explored during a phase I trial, in 24 patients with prostate cancer, on day 1 at doses between 1.45 mg/m² and 2 mg/m², i.e. above the recommended dosage (1.3 mg/m²) (15). The kinetic parameters of bortezomib in adult patients determined after the first injection are presented in Table I. Linearity based on the relationship between dose and the estimated peak concentration (Cmax) could not been established given the large variability and analytical difficulties. Total exposure as assessed from the area under the plasma concentration-time curve (AUC0-24h) increased 1.26-fold over the studied dose range (1.45-2 mg/m²). Bortezomib pharmacokinetics were best described by a two-compartment model. The estimated apparent volume of distribution (Vd) was very large (721-1270 L). The terminal half-life ranged between 10 h and 31 h (calculated over a 24 h period) and the systemic clearance ranged from 1095 mL/min and 1866 mL/min (15).
Pharmacokinetics of bortezomib have been examined in 24 patients with myeloma on day 1 and 11 of cycles 1 and 3, at 1 and 1.3 mg/m² (19). Data, reported in an abstract form, are summarised in Table I. The results are consistent with those from the phase I study (15). A 6-fold decrease of the systemic clearance upon repeated dosing (from cycle 1 to cycle 3) associated with a prolongation of the terminal half-life were observed at each dose level. (19). This finding has currently had no impact on the dosing regimen.

Special Considerations

Children. Bortezomib is not approved for use in children. A phase I trial was conducted in 11 children aged 5-17 years with various refractory solid tumors but no kinetic study was performed (24).

Renal dysfunction. Renal dysfunction is a frequent complication of multiple myeloma. The impact of nephropathy on the pharmacokinetics of bortezomib is not yet reported. Retrospective studies have analyzed the impact of renal impairment on the use of bortezomib in advanced myeloma (25, 26). Among 10 patients with creatinine clearance below 30 mL/min, 7 completed the 8-cycle protocol with 4 receiving the full dosage (1.3 mg/m²) and 3 receiving a reduced dose (1 mg/m²) (25). Based on the results obtained in 24 patients with renal failure (23 requiring dialysis), Chanan-Khan et al. (26) indicated that bortezomib was given safely. The patients received a median of 5 cycles and 20/24 were administered the recommended dosage (1.3 mg/m²) (26). At the present time, no accurate administration guidelines are included in the prescribing information. Besides the close monitoring of the patient, the package insert recommends a reduction of the dose if the creatinine clearance falls below 30 mL/min.

Hepatic dysfunction. As seen above, bortezomib undergoes hepatic biotransformation but the overall contribution of liver clearance to elimination is not known. No dosing recommendations are yet available for patients with liver dysfunction.

Factors Influencing Pharmacokinetics

Pharmacokinetics of bortezomib in adult patients with prostate cancer or myeloma were characterized by a very large interpatient variability (15, 19). The coefficients of variation (CV) for clearance were above 45% (19). Sources of variability have not yet been explored but may in part be related to analytical limitations.

Like for numerous other anticancer agents, body surface area did not appear to influence bortezomib clearance, suggesting that it could be tested given at a fixed dose (15). In a general way and in the absence of significant impact of body size (weight or surface area) on pharmacokinetics and pharmacodynamics, anticancer drugs should be given at a fixed dose because it is

Table I. Pharmacokinetic parameters for intravenous bortezomib in adults. Results as means (SD).

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Duration of study (mg/m²)</th>
<th>Cmax (µg/L)</th>
<th>Vd (L)</th>
<th>AUC (µg/L.h)</th>
<th>Cl (mL/min)</th>
<th>t1/2 (h)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>24 h 1.45 (day 1/cycle 1)</td>
<td>80.4 (72.5)</td>
<td>721 (155)</td>
<td>43.8 (20.8)</td>
<td>1255 (853)</td>
<td>10.4 (9.79)</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>24 h 1.6 (day 1/cycle 1)</td>
<td>43.7 (78.6)</td>
<td>969 (473)</td>
<td>39.3 (18.6)</td>
<td>1866 (2100)</td>
<td>31.3 (46.1)</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>24 h 1.8 (day 1/cycle 1)</td>
<td>11.2</td>
<td>1030</td>
<td>48.4</td>
<td>1095</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>24 h 2 (day 1/cycle 1)</td>
<td>36 (24.2)</td>
<td>1270 (435)</td>
<td>55.3 (19.4)</td>
<td>1061 (496)</td>
<td>13.2 (10.4)</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>NR 1 (day 1/cycle 1)</td>
<td>210 (60.7)</td>
<td>220 (77)</td>
<td>NR</td>
<td>926 (346)</td>
<td>2.8 (0.7)</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>48 h 1 (day 1/cycle 1)</td>
<td>56.7 (36.3)</td>
<td>1976 (2498)</td>
<td>26.5 (12.4)</td>
<td>1700 (800)</td>
<td>30.7 (44.8)</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>48 h 1 (day 11/cycle 1)</td>
<td>106.2 (46.7)</td>
<td>1659 (752)</td>
<td>82.8 (35.9)</td>
<td>383 (296)</td>
<td>78.9 (50.9)</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>48 h 1 (day 1/cycle 3)</td>
<td>66.5 (42.6)</td>
<td>1852 (951)</td>
<td>66.4 (24.1)</td>
<td>533 (316)</td>
<td>39.9 (14.4)</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>48 h 1 (day 11/cycle 3)</td>
<td>83.9 (69.3)</td>
<td>3294 (2993)</td>
<td>101.6 (58.2)</td>
<td>250 (231)</td>
<td>193 (169)</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>48 h 1.3 (day 11/cycle 1)</td>
<td>112 (122)</td>
<td>2015 (2974)</td>
<td>34.6 (19.8)</td>
<td>1860 (1226)</td>
<td>11.5 (12.7)</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>48 h 1.3 (day 11/cycle 3)</td>
<td>88.6 (47.6)</td>
<td>2415 (1711)</td>
<td>82.4 (28.6)</td>
<td>466 (330)</td>
<td>75.6 (49.9)</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>48 h 1.3 (day 1/cycle 3)</td>
<td>120.3 (70.7)</td>
<td>2059 (1231)</td>
<td>79.4 (24.5)</td>
<td>535 (256)</td>
<td>49.1 (34.6)</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>48 h 1.3 (day 11/cycle 3)</td>
<td>114.9 (98.3)</td>
<td>2505 (1641)</td>
<td>85.2 (18.7)</td>
<td>303 (153)</td>
<td>108.6 (64.8)</td>
<td>19</td>
</tr>
</tbody>
</table>

Cmax: plasma concentration peak; Vd: volume of distribution; AUC: area under the serum concentrations-time curve from 0 to 24 or 48 h; Cl: systemic clearance; t1/2: terminal half-life; NR: not reported.
obviously more convenient and may even be safer as it
obviates the need for dose calculation. A fixed dose of
bortezomib (approximately 2.3 mg) could reconsider the
current dosage of the vial (3.5 mg).

Pharmacodynamics

Pharmacodynamics deals with the relationship between
pharmacokinetics and the clinical effects (therapeutic or
toxic). The clinical relevance of bortezomib kinetic
variability is unknown in patients with myeloma or mantle
cell lymphoma. Whether exposure might correlate with
toxic effects (platelet or neurological toxicity) or
inadequate response has not been studied at the
therapeutic dose (1.3 mg/m²).

As a surrogate, a relationship between pharmacokinetics and
the inhibition of the enzymatic target (the 20S proteasome)
in blood has been sought in patients with prostate cancer at various time points (1, 6 and 24 h post
dosing) over the 1.45-2 mg/m² dose range, on day 1 of cycle
1 (15). The duration of enzymatic inhibition following
bortezomib injection appeared short. The maximal effect
was observed at 1 hour (approximately 70% inhibition
whatever the dosage) and the partial recovery of activity
began after 6 h. The 20S proteasome activity inhibition was
homogeneous at 1 h post-dose and was not related to the
high (8-fold) variability of plasma concentration (15). It
should be stressed that the kinetic variability was also due
to the different dosages. Overall, the 20S proteasome
inhibition in blood cells was associated neither with the
kinetic variability nor the dosage in the supratherapeutic
range 1.45-2 mg/m². The eventual relation between
enzymatic inhibition and therapeutic activity is not known.

Drug-drug Pharmacokinetic Interactions

Pharmacokinetic interactions commonly occur via drug
metabolising enzymes, drug transporters or orphan nuclear
receptors. The fact that bortezomib interferes with protein
degradation might lead to nonclassical mechanisms of
interactions.

Interactions with pharmacokinetic molecular determinants.
Bortezomib did not inhibit the activities of the isoenzymes
CYP3A4/5, CYP2C9, CYP2D6 or CYP1A2 in human liver
microsomes. It was shown to be a weak inhibitor of the
isoenzyme CYP2C19 (concentration leading to a 50%
decrease in activity, IC₅₀ 18 µM or 6.91 mg/L) (27). In
addition, the metabolite M1 was a weak inhibitor of CYP2C9
and CYP2C19, and M2 a weak inhibitor of CYP2C19 (27).
As far as the major drug metabolising enzymes (the CYP
superfamily) are concerned, bortezomib is unlikely to inhibit
the metabolism of a co-administered drug.

Little data have been published regarding interactions of
bortezomib as a substrate or an inhibitor with drug
transporters (i.e., P-glycoprotein, P-gp or ABCB1). In the
case of anticancer agents, drug transporters often constitute
both molecular pharmacokinetic determinants, healthy
tissues, and factors associated with cellular resistance,
tumor cells. Leukemic cells overexpressing P-gp exhibited
decreased in vitro sensitivity (2-fold) to bortezomib and this
low level of resistance was attenuated by the P-gp blocker
PSC-833 (28). Nevertheless, it is not known if bortezomib is
really transported by P-gp i.e., if P-gp is actually involved in
its distribution or elimination. Furthermore, it remains to
be seen whether bortezomib is an inhibitor of P-gp drug
transport. Besides the classical substrate/inhibitor
interactions, bortezomib might affect P-gp function due to its
mechanism of action. Indeed, proteasome inhibition has
been shown to block P-gp maturation and function (29).
However, the direct impact of bortezomib on P-gp function
has not been investigated. Bortezomib cytotoxicity is not
affected by the expression of multidrug resistance protein 1
(MRP1 or ABCC1) or breast cancer resistance protein
(BCRP or ABCG2) in vitro suggesting that these
transporters may not be involved in its disposition (28).

There is little information on the eventual induction
potential i.e., increased expression of enzymes or transporters
of bortezomib. Interactions as a ligand or an activator with
orphan nuclear receptors, such as the pregnane X receptor or
the constitutive androstane receptor, have not yet been
studied. In addition to induction via activation of these
transcriptional factors, elevated enzyme activity might occur via
inhibition of degradation. Indeed, CYP3A4, one of the most
important drug metabolising enzyme, is degraded, in vitro, via
the proteasomal pathway (30). However, bortezomib did not
affect CYP3A4 activity as assessed by the erythromycin breath
test in 14 patients (31). An elevated expression of CYP3A4
related to proteasome inhibition is not anticipated.

**Exploration of interactions in the clinical setting.** To date, no
drug-drug interactions involving bortezomib have been
reported. Due to its metabolic profile, bortezomib is
potentially susceptible to some kinetic interactions.
Concomitant drugs may alter the exposure to bortezomib but
based on the current knowledge, it is improbable that
bortezomib changes the pharmacokinetics of co-administered
drugs. Bortezomib is officially given as a single agent in
pretreated myeloma or mantle cell lymphoma and therefore
no interaction is expected with other anticancer drugs.
Nevertheless, in myeloma, bortezomib was tested combined
with other anticancer drugs such as melphalan, doxorubicin,
thalidomide or lenalidomide (32-35). These drugs have not
been shown to inhibit CYP isoenzymes and are unlikely to
alter bortezomib kinetics. Besides chemotherapeutic agents,
CYP3A4 inhibitors such as antifungal azoles (itraconazole,
voriconazole, posaconazole) or CYP3A4 inducers (rifampin, phenytoin) might affect bortezomib concentrations. It has to be remembered that bortezomib metabolism involves multiple CYP, thus reducing the impact of induction or inhibition of any sole isoenzyme.

As described previously, bortezomib is unlikely to alter the disposition of a co-administered agent. Supko et al. (18) reported, in an abstract, that bortezomib did not influence the pharmacokinetics of irinotecan or its active metabolite SN38 in 11 patients, based on a historical control. Likewise, and in line with the absence of interaction with CYP3A4 activity, docetaxel clearance was not affected by bortezomib in 14 patients (31).

**Conclusion**

The clinical pharmacokinetics of bortezomib are little documented partly due to analytical difficulties. Overall, the kinetic profile is characterized by a large volume of distribution and a high systemic clearance. The plasma elimination rate partly supports the current dosage schedule (twice weekly for 2 of every 3 weeks) mostly based on tolerance. The excretion routes remain to be determined as well as the contribution of biotransformation. No drug - drug interactions have been reported but some might be expected given the metabolic profile of bortezomib. In addition, investigations regarding the behaviour of bortezomib towards drug transporters as a substrate or an inhibitor are warranted to further extend the knowledge on its disposition and on the risk of interactions with coadministered drugs.

**References**


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