Phase I Study of Bortezomib in Refractory or Relapsed Acute Leukemias

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ABSTRACT

Bortezomib (Velcade, formerly PS-341) is proteasome inhibitor with documented antitumor activity in multiple myeloma and other lymphoid malignancies. We performed a Phase I study to investigate the maximum tolerated dose and dose-limiting toxicity of bortezomib in patients with acute leukemias refractory to or relapsing after prior therapy. Fifteen patients were treated with 0.75 (n = 3), 1.25 (n = 7), or 1.5 (n = 5) mg/m2 bortezomib administered twice weekly for 4 weeks every 6 weeks. Dose-limiting toxicity included orthostatic hypotension (n = 2), nausea (n = 2), diarrhea (n = 1), and fluid retention (n = 1), all at 1.5 mg/m2 bortezomib. Proteasome inhibition was dose dependent and reached 68% at 1.5 mg/m2 bortezomib. Peak inhibition was observed 1 h after treatment and returned to near baseline levels by 72 h after treatment. Incubation of blast cells with bortezomib in vitro showed induction of apoptosis in three of five patients investigated. We conclude that the maximum tolerated dose of bortezomib in patients with acute leukemia is 1.25 mg/m2, using a twice-weekly for 4 weeks every 6 weeks schedule. The in vitro evidence of antileukemia and transient hematological improvements observed in some patients warrants further investigation of bortezomib in acute leukemias, probably in combination with other agents.

INTRODUCTION

The ubiquitin-proteasome pathway is the most important intracellular pathway for protein degradation (1, 2). It consists of a multicatalytic structure, 26S, which comprises a core 20S unit composed of 28 subunits and two regulatory 19S units. Protein substrates for this system are “marked” with a ubiquitin chain that is recognized by the regulatory chain (3). The proteasome complex then degrades the ubiquitinated protein, releasing peptides and free ubiquitin. Proteolytic degradation of damaged, oxidized, or misfolded proteins is part of the “housekeeping” role of the 26S proteasome (4). The 26S proteasome also plays a vital role in degrading regulatory proteins that govern cell cycle, transcription factor activation, apoptosis, and cell trafficking (4, 5). A number of key regulatory proteins are temporarily degraded during the cell cycle by the ubiquitin-proteasome pathway. The ordered degradation of these proteins is required for the cell to progress through the cell cycle and undergo mitosis. Key regulatory proteins degraded by this system include p53, cyclins, and the cyclin-dependent kinase inhibitors p27Kip1 and p21 (6, 7). Furthermore, the ubiquitin-proteasome pathway is required for transcriptional regulation. Nuclear factor (NF)-κB is a key transcription factor (8) whose activation is regulated by proteasome-mediated degradation of the inhibitor protein IκBα (9). NF-κB has several tumor-promoting actions and is constitutively activated in neoplastic cells from solid tumors and hematological malignancies (10–16). Cell adhesion molecules such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 are regulated by NF-κB (17) and involved in tumor metastasis and angiogenesis in vivo. In addition, activated NF-κB has antiapoptotic activity, and inhibition of NF-κB induces apoptosis in several malignant cell types (18, 19). Thus, proteasome inhibition has become an important therapeutic strategy in cancer treatment.

Bortezomib (formerly PS-341, Velcade; Fig. 1) is a dipeptidyl boronic acid analog with potent and selective, reversible proteasome inhibitory activity (20). Bortezomib has demonstrated significant activity against a broad range of human tumor cells (21), as well as in animal models of human prostate cancer (22), breast cancer (23), squamous cell carcinoma (24), and T-cell leukemia (25), among others. A dose-dependent proteasome inhibition has been observed to produce significant toxicity in animal models when inhibition exceeds 80% (22). The inhibition usually recovers within 72 h. Bortezomib is the first proteasome inhibitor to be tested in the clinic in several neoplasias. We conducted a Phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of bortezomib in patients with refractory or relapsed acute leukemias.

PATIENTS AND METHODS

Patient Selection. Patients were eligible for enrollment if they had acute myeloid leukemia, acute lymphoblastic leukemia, or high-risk myelodysplastic syndrome, including refractory anemia with excess blasts and refractory anemia with excess blasts in transformation. In all cases, induction chemo-
therapy had failed to induce complete remission (CR), CR had lasted <1 year, or prior salvage therapy had failed. Other eligibility criteria included: (a) age ≥ 18 years; (b) Eastern Cooperative Oncology Group performance status ≤ 2; (c) bilirubin < 1.5 mg/dl; (d) alanine aminotransferase or aspartate aminotransferase < 150 IU/liter; (e) creatinine ≤ 1.5 mg/dl; and (f) no chemotherapy for at least 2 weeks before enrollment, although the use of hydroxyurea was permitted up to 24 h before the start of bortezomib therapy if patients had rapidly proliferative disease. Patients were excluded if they were likely to benefit from allogeneic bone marrow transplantation, being treated with other investigational agents, or had uncontrolled intercurrent illness. Patients with brain metastases, other central nervous system disease, or human immune deficiency virus were also excluded.

Drug Administration. Bortezomib was provided by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, in sterile, single-use, 3.5-mg vials containing 3.5 mg of bortezomib as a lyophilized powder with 3 mg of mannitol USP. Each 3.5-mg vial was reconstituted with 3.5 ml of normal saline USP, so that the concentration of bortezomib in the solution was 1 mg/ml. Bortezomib was administered twice a week (Tuesday/Friday or Monday/Thursday) for 4 weeks every 6 weeks. Patients received the drug as an i.v. bolus over 3–5 s. The starting dose was 0.75 mg/m², and dose escalation proceeded as per the Continual Reassessment Method (26). Patients who showed no ≥grade 3 toxicity were eligible to receive a second course. If ≤grade 2 toxicity had been observed with the first course, the second course was escalated by one dose level; otherwise the second course was administered at the same dose once grade 2 toxicity resolved completely. Patients received prophylactic antibiotics (quinolones), antifungals (fluconazole), and antivirals (acyclovir or valacyclovir), as well as RBCs and platelet transfusions, according to institutional guidelines.

Toxicities were evaluated using the revised National Cancer Institute Common Toxicity Criteria version 2.0. DLT was defined as any ≥grade 3 adverse event. Specifically, nonhematological DLT was defined as any grade 3 or 4 toxicity (as defined by National Cancer Institute common criteria). Nausea and vomiting were considered DLTs only if they were not responsive to antiemetic therapy. Hematological DLT was defined as pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for ≥6 weeks after the start of a course.

Pretreatment and Follow-Up Studies. Pretreatment evaluation included a history and physical exam; assessment of signs, symptoms, and performance status; complete blood counts, platelet count, differential, blood chemistry, and coagulation studies; and bone marrow aspiration. During the study, complete blood counts, platelet count, and differential were performed two to three times weekly until recovery of counts. Blood chemistry was done weekly until recovery, and then it was done every 2–4 weeks. Marrow aspiration was performed on day 28 and every 3–14 days thereafter as clinically indicated until remission, after which it was planned every 1–3 courses.

Evaluation of response was performed every 6 weeks. Complete remission was defined as platelet count > 100 × 10⁹/liter, neutrophil count > 1 × 10⁹/liter, and a cellular marrow with blast count ≤ 5%. Hematological improvement was defined as platelet count > 30 × 10⁹/liter, neutrophil count > 0.5 × 10⁹/liter, and/or blast count ≤ 5%. Progressive disease was defined as an increase of the circulating blasts count by ≥100% and to a level > 10 × 10⁹/liter. Any disease state not meeting the criteria for any of these three response categories was considered stable disease. Treatment was stopped if any of the following events occurred: disease progression; intercurrent illness that prevented further administration of treatment; unacceptable toxicity; receipt of a bone marrow transplant; or patient withdrawal from the study.

Proteasome Inhibition. 20S Proteasome enzyme activity was measured in whole blood using the assay described by Lightcap et al. (27). Briefly, the assay measures the pharmacological activity of bortezomib at its biochemical target site, the proteasome, as determined by the chymotryptic:tryptic ratio assay (which measures activity at the chymotryptic and tryptic sites on the proteasome) and the specific activity assay (which measures activity at the chymotryptic site only). For whole blood samples, all cells were washed and lysed, and residual 20S proteasome activity was measured using the spectrofluorometric kinetic enzyme assay. Blood samples for the 20S assay were taken at baseline and then at multiple time points after administration of bortezomib. The 20S proteasome activity was reported as a chymotryptic:tryptic ratio, and the extent of inhibition was reported as a percentage of the baseline values.

Quantification of Apoptosis. Apoptosis was assessed by propidium iodide staining and fluorescence-activated cell-sorting analysis as described previously (28, 29). After incubation with various agents in vitro, cells were pelleted by centrifugation and resuspended in PBS containing 50 μg/ml propidium iodide, 0.1% Triton X-100, and 0.1% sodium citrate. Samples were stored at 4°C for 16 h and vortexed before fluorescence-activated cell-sorting analysis (FL-3 channel; FACScan; Becton Dickinson, Mountain View, CA).

Statistical Considerations. The Continuous Reassessment Method was used in standard fashion in this Phase I study to determine the MTD. The principal end point was the occurrence of ≥grade 3 toxicity. MTD was defined as the dose associated with a toxicity probability closest to 0.2 after a maximum of 30 patients were treated. The initial mean toxicity probabilities at the four levels (−1, 1, 2, and 3) were set (prior)
Table 1  Patient characteristics for 15 patients treated with bortezomib

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 (18–71)</td>
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<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML*</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>3</td>
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<tr>
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<td>Cytogenetics</td>
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<tr>
<td>−5/−7</td>
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<td></td>
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<tr>
<td>Diploid</td>
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<tr>
<td>1st relapse</td>
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<td>2nd or subsequent relapse*</td>
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<td>Duration of 1st CR (wks)</td>
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<tr>
<td>No. of prior salvage failures</td>
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<td>WBCs (×10^9/liter)</td>
<td>2.3 (0.7–41.4)</td>
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<tr>
<td>ANC (×10^9/liter)</td>
<td>0.6 (0–3.8)</td>
<td></td>
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<tr>
<td>Platelets (×10^9/liter)</td>
<td>38 (4–171)</td>
<td></td>
</tr>
</tbody>
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*AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; IM, insufficient metaphases; CR, complete remission; ANC, absolute neutrophil count.

at 0.1, 0.2, 0.3, and 0.5. Patients were entered in cohorts of 2 patients and started at level 0. To be evaluable for dose escalation considerations, patients should have received at least 4 doses of bortezomib unless removed from the study because of toxicity. At least one patient had to be evaluated at each dose level for 2 weeks before proceeding to the next dose level with a new cohort of patients, although the “look ahead” option was permitted. As response (≥grade 3 toxicity/<grade 3 toxicity) was observed in each cohort, the posterior probability of toxicity was updated, and the next cohort was treated at the dose with posterior toxicity probability closest to 0.2, and skipping a dose level was allowed. Updates were made using the CRM 0.5 software program.

RESULTS

Patient Characteristics. Fifteen patients with acute myeloid leukemia (n = 11), acute lymphoblastic leukemia (n = 3), or myelodysplastic syndrome (n = 1) were treated (Table 1). Their median age was 59 years (range, 18–71 years). Two patients had never achieved a CR, and the median duration of the first CR for the other 13 patients was 34 weeks (range, 3–588 weeks). Ten patients had failed 1–4 prior salvage attempts with other treatment regimens (median, 1.5 salvage attempts).

Dose Escalation. The starting dose of bortezomib was 0.75 mg/m² for three patients (two of whom were evaluable), 1.25 mg/m² for seven patients (six of whom were evaluable), and 1.5 mg/m² for five patients (five of whom were evaluable). Patients received a median of 5 doses of bortezomib (range, 2–5 doses). Inevaluable patients received only 2 doses (at 0.75 mg/m²) and 3 doses (at 1.25 mg/m²), respectively, because of rapidly progressive disease. The most common cause for discontinuation of therapy for evaluable patients was progressive disease, except for those described below, who discontinued therapy because of toxicity. The 0.9 mg/m² dosage was skipped as permitted by the study design according to the Continuous Reassessment Method. Only one patient received a second cycle of bortezomib. This patient received 1.25 mg/m² bortezomib for the first cycle and 1.5 mg/m² bortezomib for the second cycle.

Toxicity. Toxicity is summarized in Table 2. The most common nonhematological toxicities were hypokalemia (n = 7), mucositis (n = 6), fluid retention (n = 6), fatigue (n = 5), and diarrhea (n = 4). No bortezomib-related, ≥grade 3 toxicity was observed among the three patients treated at 0.75 mg/m² or the seven patients treated at 1.25 mg/m². DLTs observed at the 1.5-mg/m² dose level included orthostatic hypotension (n = 2), nausea (n = 2), diarrhea (n = 1), hypokalemia (n = 1), and fluid retention (n = 1). One more patient, who received a second cycle of bortezomib at 1.5 mg/m² (first cycle of bortezomib at 1.25 mg/m²), experienced orthostatic hypotension. In addition, one patient treated with 1.5 mg/m² bortezomib had grade 3 chest pain that was noncardiogenic in origin.

Orthostatic hypotension was suggestive of an autonomic dysregulation. Two patients developed orthostatic hypotension during their first cycle of therapy while they were having gastrointestinal toxicity (grade 3 diarrhea, nausea, and/or vomiting) and dehydration. The hypotension persisted despite fluid resuscitation and resolution of the gastrointestinal symptoms. The symptoms resolved in one patient 7 days after the last dose of bortezomib with the use of fludrocortisone acetate; the second patient had persistent hypotension for 45 days when he decided to pursue hospice care only. A third patient developed orthostatic hypotension on the second cycle of bortezomib. The first cycle was given at 1.25 mg/m² with no significant toxicity. The second cycle, which was given at 1.5 mg/m², resulted in orthostatic hypotension and syncope without gastrointestinal toxicity that lasted for >45 days.

The other grade 3 toxicities at the 1.5-mg/m² dose included a patient who developed grade 3 nausea and vomiting and grade 2 diarrhea, with dehydration and grade 3 hypokalemia, after 5 doses of bortezomib that led to grade 2 renal dysfunction. Despite adequate hydration, the renal dysfunction continued with only mild improvement, and she developed grade 3 fluid overload. Eventually, the renal dysfunction resolved 7 days after the last dose of bortezomib, with slow improvement of the fluid retention. One patient presented to the emergency room with sudden-onset chest pain after the third dose of bortezomib at 1.5 mg/m². A complete cardiac work-up was initiated, and a myocardial infarction was ruled out. The symptoms were considered to be unrelated to bortezomib, noncardiac in origin, and more suggestive of musculoskeletal origin. Indeed, the pain resolved rapidly after administration of nonsteroidal anti-inflammatory agents, and the patient was able to complete the first cycle (8 doses) of bortezomib with no other toxicity.

Pharmacodynamics. A total of 10 patients were evaluated for changes in proteasome enzyme activity induced by bortezomib. Maximum inhibition of 20S proteasome activity, related to pretreatment values, was observed 1 h after administration of bortezomib. The extent of inhibition was dose dependent (Table 3), with median values of 44%, 66%, and 68% for the three dose groups of 0.75, 1.25, and 1.5 mg/m², respectively. The time course of 20S inhibition is reported on Fig. 2, using the three data points for which sufficient samples were collected.
After peak inhibition was observed at 1 h post-dose, the effect of bortezomib appeared to be rapidly reversible, with approximately 50% of enzyme activity recovered after 24 h and a further return toward pretreatment levels at 72 h post-dose (dose interval).

**Induction of Apoptosis.** Peripheral blood mononuclear cells were also harvested from five of the patients on the trial to test their sensitivities to bortezomib-induced apoptosis in vitro. Cells taken from three of the patients displayed significant levels (>50%) of apoptosis after exposure in vitro to 10 μM bortezomib after 24 h. One of these three patients had a significant reduction in peripheral blood blasts.

**Response.** Five patients met criteria for hematological improvement: four for a decrease in blast count; and one for improvement in neutrophils. Three patients had a >50% decrease in peripheral blasts to ≤5%. One patient treated at the 1.25-mg/m² dose showed a reduction in peripheral blasts from 65% to 5%, and two patients treated at the 1.5-mg/m² dose showed a reduction from 26% to 2% and from 33% to 2%, respectively. Additionally, one patient receiving the 1.25-mg/m² dose showed a reduction in bone marrow blasts, from 20% to 4% (no peripheral blasts at baseline). One additional patient who started with no peripheral blasts had a significant improvement in neutrophils during therapy from 0.475 × 10⁹/liter to 10.6 × 10⁹/liter, with no improvement in thrombocytopenia or anemia. These improvements were all transient, with eventual recurrence of the initial counts, usually during the time off therapy. In addition, all four patients who started with a WBC count of >4 × 10⁹/liter had a rapid progression of the disease and were unable to receive more than 5 doses of bortezomib. The 11 patients who started with a WBC count of ≤4 × 10⁹/liter were more likely to keep a stable WBC count through therapy, which allowed continuation of bortezomib; the exceptions were 2 patients treated at the lowest dose, who had a rapid increase in WBC count after 2 and 5 doses, respectively.

**DISCUSSION**

The ubiquitin-proteasome pathway is an important intracellular system for protein degradation. The ATP-dependent, multicatalytic protease, 26S, is central to this pathway, serving to degrade damaged, oxidized, or misfolded proteins as well as proteins that regulate the cell cycle, transcription factor activation, and apoptosis. Therefore, the 26S proteasome represents a new and potentially important target for chemotherapy. Bortezomib has potent and selective, reversible proteasome inhibitory activity (20), and its ability to disrupt the ubiquitin-proteasome pathway by inhibition of 26S may make it a valuable therapeutic agent. In this study, we investigated the MTD of bortezomib in patients with refractory or relapsed acute leukemias or myelodysplastic syndrome.

The MTD identified in this study was 1.25 mg/m² administered twice weekly for 4 weeks every 6 weeks. None of the 7 patients treated at this dose experienced any grade 3 toxicity. In contrast, four of five patients treated at the highest dose (i.e., 1.5 mg/m²) experienced grade 3 toxicity. The DLT was orthostatic hypotension observed in three patients, including one patient...
receiving a second cycle of bortezomib at 1.5 mg/m². Although in two patients the onset of this toxicity coincided with dehydration associated with gastrointestinal toxicity, it persisted after the fluid balance had been restored, suggesting a primary mechanism. In addition, one patient had gastrointestinal toxicity leading to renal dysfunction and fluid retention. Orthostatic hypotension has not been reported as dose-limiting in other Phase I studies with bortezomib in hematological malignancies [except acute leukemias (30)] and solid tumors (31). However, one patient in the study by Orlowski et al. (30) developed this toxicity after additional cycles of bortezomib. Our patients experienced this toxicity at a dose (1.5 mg/m²) higher than the highest dose investigated in the study of Orlowski et al. [the highest dose level was 1.38 mg/m² (30)]. A dose of 1.56 mg/m² was administered to 12 patients with solid tumors by Aghajanian et al. (31) with no reports of orthostatic hypotension, although diarrhea and peripheral neuropathy were dose-limiting (two patients each). However, bortezomib was administered in that study for 2 weeks every 3 weeks. It is possible that a more prolonged administration (i.e., 4 weeks every 6 weeks), such as that used in the current report, may induce additional toxicity. At the time this study was designed, the ideal schedule for bortezomib was still unknown; thus, this study and other studies (30) used a more prolonged schedule to try to achieve a more durable proteasome inhibition. Due to the increased toxicity with more prolonged schedules such as the one used here, the currently recommended schedule is twice weekly for 2 weeks every 3 weeks.

This MTD in our trial is higher than that reported for bortezomib in other refractory hematological malignancies (excluding acute leukemias) using a similar schedule (30). Orlowski et al. (30) identified the MTD at 1.04 mg/m². However, the most common DLT was hematological toxicity including neutropenia, thrombocytopenia, and anemia that occurred in six of seven patients treated at 1.2 mg/m². Our study included patients with acute leukemias; therefore, these hematological toxicities did not apply because, by the nature of their disease, all patients had neutropenia and/or thrombocytopenia at baseline and because persistent myelosuppression is mostly irreversible in the setting of persistent or progressive leukemia that all our patients had. Only one patient in our study started with a platelet count of >50 × 10⁹/liter (70 × 10⁹/liter), which decreased with therapy and had not recovered to baseline after ≥6 weeks (31 × 10⁹/liter on day 78, when taken off study for progressive disease). Nonhematological toxicities seen by Orlowski et al. (30) at this dose level included malaise (n = 1) and hypokalemia (n = 1). Although malaise and hypokalemia were also common in our study, they were most frequently ≤grade 2 and thus not dose-limiting. Both these studies used a schedule of twice-weekly administration for 4 weeks every 6 weeks. However, we also have to consider that the confidence interval for the actual toxicity at the 1.25-mg/m² dose level is wide because of the small number of patients. This is particularly important, considering that there was significant toxicity at the next dose level with an increment of only 15% of the dose. The study of Aghajanian et al. (31) in patients with solid tumors used a schedule of twice-weekly administration for 2 weeks every 3 weeks. Using this schedule, a dose of up to 1.56 mg/m² was administered with nonhematological DLT in 4 of 12 patients. This schedule is now recommended, at a dose of 1.3 mg/m².

There was evidence of antileukemia activity in four patients treated in the present study. This was modest and transient, manifested by a decrease of peripheral blood or bone marrow blasts. Proteasome inhibition could be demonstrated in all patients. In addition, in some patients, bortezomib administration led to in vivo apoptosis of the leukemia cells. Furthermore, in vitro analyses revealed that bortezomib stimulated high levels of apoptosis in three of five patients evaluated. Only one of these patients had some clinical evidence of antileukemia effect (peripheral blood blasts decreased from 26% to 2%). Thus, there is some discordance between the induction of apoptosis and the reduction in blasts. It might be more meaningful to measure apoptosis and proteasome inhibition in the bone marrow. Unfortunately, this was not done on this study and would be important to consider in future trials. Also, although the sample size included in this analysis was very small, the data indicate that there is significant interpatient heterogeneity in intrinsic drug sensitivity. Thus, our results show evidence of biological activity of bortezomib in leukemia. However, the clinical benefit was minor. This was a population of heavily pretreated patients with high-risk features in which the expected CR rate is 1% to 10% (32), and the lack of true CRs is not unexpected. This brings the issue of an ever-increasing problem of how to evaluate the potential activity of “biological” or “targeted” therapies in patients with advanced diseases. In addition, the biological basis and molecular basis of resistance to bortezomib are not known and should be characterized so that future trials take them into account.

Patients who started with a WBC count of ≥4 × 10⁹/liter had a rapid increase in the WBC count that precluded a full cycle of therapy. Patients starting with a WBC count of <4 × 10⁹/liter were more likely to receive a full cycle of therapy. Thus, bortezomib might be better suited for more indolent diseases such as myelodysplastic syndrome or for settings such as postremission therapy in acute leukemia. Another alternative is to combine bortezomib with chemotherapy or other agents. Bortezomib can increase the sensitivity to chemotherapy in several tumor models (33–35) including agents that have anti-leukemia activity. Also, there might be potential synergy with other agents that affect the protein degradation such as 17-(Allylamino)-17-demethoxygeldanamycin (36).

We conclude that the MTD for bortezomib, administered on a twice-weekly schedule for 4 weeks every 6 weeks, is 1.25 mg/m². This is similar to the currently recommended dose (1.3 mg/m²), given on a twice-weekly schedule for 2 weeks every 3 weeks. There is some evidence of biological activity of bortezomib in this heavily pretreated population, and further investigation of bortezomib in this setting is warranted, including studies in combination with chemotherapy or other targeted agents.

REFERENCES


Correction: Article on Phase I Study of Bortezomib in Refractory or Relapsed Acute Leukemias

In the article on the Phase I Study of Bortezomib in Leukemias in the May 15, 2004 issue of *Clinical Cancer Research*, there was an error in authorship. The correct list of authors is, as follows:

Jorge Cortes, Deborah Thomas, Charles Koller, Frances Giles, Elihu Estey, Stefan Faderl, Guillermo Garcia-Manero, David McConkey, Stacey L. Ruiz, Roberto Guerciolini, John Wright, and Hagop Kantarjian.


Correction: Article on The Na+/I-Symporter Mediates Iodide Uptake in Breast Cancer Metastases and Can Be Selectively Downregulated in the Thyroid

In the article on the NIS-mediated Uptake in Breast Cancer Metastases in the July 1, 2004 issue of *Clinical Cancer Research*, in the Dosimetric Calculation section, there was an error in estimating the cumulative radiation dose. The estimated cumulative radiation dose to the thyroid and whole body for 100 mCi of $^{131}$I was 333 and 15 cGy, respectively.

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