The Emerging Role of Targeted Therapy for Hematologic Malignancies: Update on Bortezomib and Tipifarnib

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Key Words. Bortezomib • Multiple myeloma • Proteasome inhibition • Tipifarnib • Targeted therapy

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the role of bortezomib and tipifarnib in managing hematologic malignancies.
2. Identify the molecular targets and mechanisms of action of bortezomib and tipifarnib.
3. Describe the toxicities seen with bortezomib and tipifarnib.

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ABSTRACT

As therapy for hematologic malignancy evolves, new regimens and novel agents that target specific cellular processes allow a more optimistic prognosis for many patients. Bortezomib and tipifarnib are two new, targeted treatments for hematologic malignancies. Bortezomib, a proteasome inhibitor, has shown impressive efficacy in patients with relapsed multiple myeloma and as initial treatment, including before autologous stem cell transplantation. It has been studied as monotherapy and in combination with standard treatments such as dexamethasone, and with newer agents such as the immunomodulators thalidomide and lenalidomide; response is encouraging, even in patients who have relapsed after previously receiving components of a regimen as single agents. Bortezomib is generally well tolerated, including in combination with novel and conventional agents. Tipifarnib is a specific inhibitor of farnesyltransferase. Clinical trials in patients with high-risk acute leukemias and myelodysplastic syndromes have demonstrated good efficacy with tipifarnib. Continued investigation with these new, targeted treatments will further define their use as treatment options in patients with hematologic cancer.

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Disclosure of potential conflicts of interest is found at the end of this article.

**INTRODUCTION**

Among the most important treatment breakthroughs for cancer patients are therapies targeted toward specific cellular processes that are responsible for tumorigenesis, and regimens with novel combinations based on different mechanisms of action. New treatments and regimens are leading to a time when cancer is not a uniformly fatal disease, allowing many cancer patients to live active and productive lives long after initial diagnosis.

Especially promising targeted treatments have emerged for patients with hematologic malignancies. The introduction of the tyrosine kinase inhibitor imatinib in 2001 has changed the future for patients diagnosed with Philadelphia chromosome-positive chronic myelogenous leukemia. Two novel targeted therapies, one available and one under clinical investigation, are also offering new hope to patients with hematologic malignancies. Bortezomib (VELCADE®; Ortho Biotech, a division of Janssen-Cilag, Beerse, Belgium; and Millennium Pharmaceuticals, Cambridge, Massachusetts, USA), a proteasome inhibitor, is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Tipifarnib, a specific inhibitor of farnesyltransferase, is under investigation for the treatment of acute leukemias and myelodysplastic syndromes. By targeting the proteasome, bortezomib affects numerous regulatory proteins necessary for the malignant cells to proliferate, leading to apoptosis; the inhibition of farnesyltransferase affects multiple protein substrates involved in tumor cell proliferation. The different cellular targets of bortezomib and tipifarnib present an interesting study vis-à-vis the clinical efficacy of these agents for various hematologic malignancies.

This first of two articles is based on presentations at the 13th European Cancer Conference (October 30–November 3, 2005; Paris) and highlights the most recent data available on the efficacy and safety of bortezomib and tipifarnib for the treatment of hematologic malignancies; results of clinical investigations with these agents for other tumors are also included.

**Bortezomib**

Multiple myeloma is a hematologic malignancy of B-cell origin that is generally considered incurable. There have been few significant breakthroughs in the treatment of multiple myeloma since melphalan plus prednisone became the standard treatment in the early 1960s. Approximately 20 years later, myeloablation with autologous stem cell transplantation (ASCT) became the treatment of choice for patients who were able to tolerate the high-dose chemotherapy, and ASCT remains standard initial treatment today for younger patients. However, when relapses invariably occur, patients receive numerous additional treatments, including high-dose dexamethasone alone [1–3] or in combination with vincristine and doxorubicin. Since 1999, the immunomodulatory compound thalidomide has been shown to have activity against multiple myeloma [4–7], and most recently an analog of thalidomide, lenalidomide, has been under investigation [8–10].

Bortezomib is a proteasome inhibitor that is the first in a new class of agents [11–13]. By inhibiting the proteasome, bortezomib specifically targets the myeloma cell and inhibits its binding of the myeloma cell to the stroma, thereby affecting the microenvironment [11].

**Mechanism of Action**

The proteasome is a large multiprotein particle present in all eukaryotic cells and is the primary component of the protein degradation pathway of the cell known as the ubiquitin-proteasome pathway. The proteasome consists of two functional components: a 20S core complex responsible for the proteolytic activity and a 19S regulatory subunit. The proteasome is central to processes such as cell-cycle regulation, apoptosis, and angiogenesis; it is conceivable, therefore, that blockade of proteolytic activity would result in cell death.

Briefly, proteasome inhibition by bortezomib is due to rapid but reversible binding to a single threonine in the active site of the 20S proteolytic core [11, 13, 14], which leads to increased apoptosis and affects a number of important regulatory proteins, including p53, nuclear factor κB (NF-κB), and Bax, a proapoptotic inhibitor of Bcl-2. Bortezomib also downregulates cascades triggered by interleukin-6 (IL-6; Fig. 1) [15]. Tumor cells seem to be considerably more sensitive to proteasome inhibition than normal cells [16], and numerous studies have shown that proteasome inhibition induces apoptosis in malignant cells [11–13].

**Clinical Trials**

Clinical trials of bortezomib (Table 1) have proven its efficacy in patients with multiple myeloma and have demonstrated the overall safety of targeted therapy. Two phase II trials, SUMMIT [17] and CREST [18], demonstrated that bortezomib, alone or in combination with dexamethasone, is active in patients with relapsed multiple myeloma and established the dosage regimen as 1.3 mg/m² on days 1, 4, 8, and 11 in 3-week cycles. After these studies, a multicenter phase III trial, APEX [19], was conducted to compare the efficacy and safety of single-agent bortezomib to high-dose dexamethasone in patients with relapsed multiple myeloma.
after one to three prior lines of therapy. Patients were randomized 1:1 to treatment with eight cycles of single-agent bortezomib (n = 333) or high-dose dexamethasone (n = 336). Because interim analysis showed significant improvement with bortezomib compared with dexamethasone, the dexamethasone arm of the study was halted, and patients in this treatment group were allowed to cross over to bortezomib.

At study end, efficacy parameters demonstrated that bortezomib is superior to high-dose dexamethasone for the treatment of patients with multiple myeloma who have had disease relapse after one to three prior therapies. Median time-to-progression (TTP), the primary study endpoint, was 189 days with bortezomib versus 106 days for dexamethasone (hazard ratio for bortezomib group, 0.55; \( p < .001 \)). Overall response rate (ORR; complete response [CR] + partial response [PR]) was 38% with bortezomib versus 18% for dexamethasone (\( p < .001 \)). Complete response was also significantly greater for bortezomib versus dexamethasone (6% vs. <1%, respectively; \( p < .001 \)), as was 1-year survival (80% vs. 66%, respectively; \( p = .003 \)). Median time-to-response (TTR) was 43 days for both treatment groups; duration of response (DOR) was greater for patients who received bortezomib compared with dexamethasone (8 months vs. 5.6 months, respectively).

In a follow-up analysis to update efficacy parameters, ORR for patients who received bortezomib increased to 43%, and improved response with longer therapy (after cycle 6) was observed in 56% of responders to bortezomib [20]. Median TTR was more rapid and median DOR was longer in patients who achieved a CR and near-CR (nCR) with bortezomib compared to patients with PR (0.8 month vs. 1.4 months, respectively, for TTR; 9.9 months vs. 7.6 months, respectively, for DOR). The results from these analyses continue to support original findings and demonstrate the clinical benefits of single-agent bortezomib in patients with relapsed multiple myeloma.

**Bortezomib Efficacy After First Relapse**

In a subgroup analysis of the efficacy of bortezomib in multiple myeloma patients who had received one previous therapy...
apy versus patients who had received two or more therapies, ORR (CR + PR) to bortezomib was significantly better than ORR to dexamethasone and was greater for patients who received bortezomib earlier in the course of treatment [19]. Overall response rate to bortezomib after first relapse was 45% versus 26% for dexamethasone ($p = .004$); after two or more relapses, ORR was 34% with bortezomib and 13% with dexamethasone ($p < .0001$).

**Bortezomib Efficacy in Special Populations**

Subanalyses of the data from APEX have demonstrated the efficacy of bortezomib in elderly patients and patients with adverse prognostic factors [21]. Bortezomib was superior to dexamethasone for TTP and ORR in patients over 65 years of age (168 days vs. 132 days, respectively; 40% vs. 18%, respectively); patients with $\beta_2$-microglobulin $>2.5$ mg/l (170 days vs. 106 days, respectively; 39% vs. 18%, respectively); and patients refractory to their last line of treatment (168 days vs. 85 days, respectively; 35% vs. 13%, respectively).

When used alone or in combination, bortezomib was shown to overcome the adverse prognostic impact of 13q deletion in a subanalysis of the phase II SUMMIT trial [22]. In this trial of extensively pretreated patients with multiple myeloma, four of seven patients (57%) with a 13q deletion by fluorescence in situ hybridization achieved an objective response. A patient with a 13q deletion plus translocation t(4,14)(p16;q32) responded to single-agent bortezomib with a 7-month remission and later responded to bortezomib in combination with dexamethasone, and dexamethasone and melphalan or doxorubicin, with remissions lasting for several months each.

**Table 1. Summary of phase II and III clinical trials with bortezomib in patients with multiple myeloma**

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<tr>
<td><strong>Design</strong></td>
<td>Open-label, multicenter</td>
<td>Open-label, multicenter, randomized; two dose levels of bortezomib</td>
<td>Open-label, multicenter, randomized to bortezomib or dexamethasone</td>
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<tr>
<td><strong>Patients</strong></td>
<td>Relapsed or refractory ($n = 202$)</td>
<td>Relapsed during/ following first-line treatment ($n = 54$)</td>
<td>Relapsed ($n = 669$)</td>
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<tr>
<td><strong>Bortezomib</strong></td>
<td>1.3 mg/m$^2$ IV on days 1, 4, 8, 11; 21-day cycle, maximum 8 cycles</td>
<td>1.0 mg/m$^2$ ($n = 28$) or 1.3 mg/m$^2$ ($n = 26$) on days 1, 4, 8, 11; 21-day cycle, maximum 8 cycles</td>
<td>Induction (8 cycles): 1.3 mg/m$^2$ IV on days 1, 4, 8, 11; 21-day cycle. Maintenance (3 cycles): 1.3 mg/m$^2$ on days 1, 8, 15, 22; 35-day cycle (275 treatment days, $n = 333$)</td>
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<tr>
<td><strong>Dexamethasone</strong></td>
<td>May be allowed$^a$</td>
<td>May be allowed$^a$</td>
<td>Induction (4 cycles): 40 mg p.o. on days 1–4, 9–12, 17–20, 35-day cycle; maintenance (5 cycles): 40 mg p.o. on days 1–4, 28-day cycle (280 treatment days; $n = 336$)</td>
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<tr>
<td><strong>Overall response</strong></td>
<td>35%</td>
<td>1.0 mg/m$^2$: 33% + Dex: 44%</td>
<td>First relapse: bortezomib, 45%; dexamethasone, 26% ($p = .004$)</td>
</tr>
<tr>
<td><strong>Phase II studies:</strong> CR + PR + MR</td>
<td>1.3 mg/m$^2$: 50% + Dex: 62%</td>
<td>Two or more relapses: bortezomib, 34%; dexamethasone, 13% ($p &lt; .0001$)</td>
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<td><strong>Phase III study: CR + PR</strong></td>
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$^a$Dexamethasone was allowed for suboptimal response (progressive disease after two cycles or stable disease after four cycles); dosage: 20 mg p.o. on day of and day after bortezomib.

Abbreviations: APEX, Assessment of Proteasome Inhibition on Extending Remission Results; CR, complete response; CREST, Clinical Response and Efficacy Study; Dex, dexamethasone; MR, minimal response; PR, partial response; SUMMIT, Study of Uncontrolled Myeloma Managed with Proteasome Inhibition Therapy.
Patients from both phase II trials [17, 18] were used to evaluate response and safety in patients with renal dysfunction [23]. Although clinical experience is limited, results suggest that bortezomib is effective, with manageable toxicity. Ten patients had creatinine clearance of \( \leq 30 \) ml per minute; seven patients completed eight cycles of bortezomib treatment (four patients received 1.3 mg/m\(^2\); three patients received 1.0 mg/m\(^2\)). Response rate (two PR and one minimal response [MR]) was similar to the overall treated population. Patients with creatinine clearance >80 ml per minute \((n = 105)\), 51–80 ml per minute \((n = 99)\), and \(\leq 50\) ml per minute \((n = 52)\) had similar rates of discontinuation and similar adverse-event profiles.

**Efficacy of Bortezomib in Previously Untreated Patients**

Two studies have been conducted that demonstrate the efficacy of single-agent bortezomib as first-line treatment in newly diagnosed patients. In a multicenter phase II study, 1.3 mg/m\(^2\) bortezomib in the usual regimen was administered as a single agent to 22 patients with previously untreated multiple myeloma; dexamethasone was not permitted [24]. Overall response rate after more than two cycles of therapy was 41% (CR in one patient [5%]; PR in eight patients [36%]); MR was noted in an additional five patients (23%), six patients (27%) had stable disease (SD), and two patients (9%) progressed.

In a second phase II trial, bortezomib 1.3 mg/m\(^2\) in the usual regimen was administered alone or with 40 mg of oral dexamethasone if patients did not achieve at least a partial response after two cycles, or had less than a complete response after four cycles [25]. For the 23 patients who completed the study and were evaluable, bortezomib was found to be highly active in the first-line treatment of multiple myeloma, with an overall major response rate of 83% (CR, 13%; nCR, 17%; PR, 53%) and minor response rate of 13%. Dexamethasone was administered to 14 patients (61%) in addition to bortezomib. An improved response after combination treatment was seen in nine patients, with six patients improving from MR to PR and three patients improving from stable disease to PR. Additionally, stem cell transplantation was successful in all attempts.

Based on the hypothesis that the effects of bortezomib and dexamethasone are additive [12], clinical trials have been conducted with this combination as induction treatment before ASCT. In a phase II study, patients \((N = 53)\) were scheduled to receive bortezomib 1.3 mg/m\(^2\) intravenously on days 1, 4, 8, and 11, and dexamethasone 40 mg orally on days 1–4 and 9–12 for the first two cycles, then days 1–4 only for the last two cycles; stem cell collection was performed immediately before cycle 4 after granulocyte colony-stimulating factor priming [26]. Efficacy for 30 patients with available data was encouraging, with an ORR of 80% (CR, 17%; very good PR, 13%; PR, 43%; minimal response, 7%). Stem cells were adequately collected from 29 evaluable patients; median CD34\(^+\) cell yield was \(7.1 \times 10^{5}/kg\) (range 2.9–33.8). For 36 patients evaluable for toxicity, 27 (75%) received the complete regimen of 16 injections. Adverse events were usually mild (grade 1–2); the most frequent adverse events were gastrointestinal symptoms (49%), fatigue (34%), peripheral neuropathy (29%), skin toxicity (26%), and thrombocytopenia (17%). Other clinical trials have shown the effectiveness of adding bortezomib to combination treatment before ASCT in previously untreated patients with multiple myeloma, including combining bortezomib with doxorubicin and dexamethasone [27], with thalidomide and dexamethasone [28], and with dexamethasone, thalidomide, cisplatinum, doxorubicin, cyclophosphamide, and etoposide (DT-PACE) [29].

Newly diagnosed elderly \((\geq 65\) years\) patients with no prior treatment for multiple myeloma were the subjects of a clinical trial of bortezomib in combination [30]. The objectives were to define the appropriate dose of bortezomib \((1.0\) and \(1.3\) mg/m\(^2\)) administered on days 1, 4, 8, 11, 22, 25, 29, and 32 in combination with oral melphalan 9 mg/m\(^2\) and prednisone 60 mg/m\(^2\) once daily on days 1–4 and to analyze efficacy and toxicity of the combination. Sixty patients were enrolled. No dose-limiting toxicity occurred, so the recommended bortezomib dose for the study was 1.3 mg/m\(^2\). Best response rate after a median of three cycles was 85% (28% CR immunofixation [CRIF]-negative; 11% CRIF-positive; 45% PR); one patient (2%) had minor response, and seven patients (13%) had stable disease. Adverse events were manageable, and the conclusion was that adding bortezomib to melphalan and prednisone could become the standard of care for elderly patients with multiple myeloma.

**Novel Combinations with Bortezomib**

Studies have shown that bortezomib-containing regimens, based on rational combinations of novel agents, can achieve significant responses. Because interactions between multiple myeloma cells and the bone marrow microenvironment may be important determinants of the response of multiple myeloma cells to therapeutic agents [31], drugs that target the multiple myeloma cell directly can be combined with drugs that target the bone marrow microenvironment. A specific example is the combination of bortezomib, a proteasome inhibitor, with an immunomodulatory agent (IMiD), such as thalidomide. Studies have shown that bortezomib directly induces apoptosis of multiple myeloma cells, despite the induction of p21 and p27 [12], and that

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thalidomide inhibits IL-6 production and downregulates key angiogenic genes in bone marrow cells [32, 33]. A recent report illustrated the effectiveness of this combination in a population of patients (N = 85) with advanced and refractory multiple myeloma [34]. In this very high-risk patient population, 52% of patients achieved at least a PR, including 12% with either CR or nCR; 68% had ≥25% M protein reduction. The regimen was well tolerated; adverse events were reported as mild or moderate.

Other combinations include bortezomib with dexamethasone or lenalidomide to trigger dual apoptotic signaling [12, 35]. Bortezomib and lenalidomide administered in different dosing combinations in patients with relapsed and refractory multiple myeloma showed promising activity in a phase I clinical trial [36]. For nine patients evaluable for response, six had MR, two had PR, and one had SD. Cell signaling studies have suggested several promising, novel combinations with bortezomib, including combination with PKI1195, a ligand of the mitochondrial benzodiazepine receptor, to target mitochondria and overcome bortezomib resistance [37–39], and combination with a histone deacetylase inhibitor to enhance blockade of ubiquitinated protein degradation [40]. Studies are also exploring combinations with inhibitors of p38 mitogen-activated protein kinase (MAPK) to downregulate heat shock protein-27 and overcome bortezomib resistance [41, 42].

**Bortezomib Treatment for Other Hematologic and Solid Tumors**

Many of the pathways mediated by proteasome inhibition in multiple myeloma operate in other types of neoplasia and bortezomib has been shown to inhibit tumor cell proliferation in non-Hodgkin’s lymphoma (NHL) and mantle cell lymphoma (MCL) [43–47]. Bortezomib treatment for lymphoma was evaluated in a phase II clinical trial that enrolled patients with follicular lymphoma (FL; n = 19); MCL (n = 23); small lymphocytic lymphoma (SLL; n = 5); and marginal-zone lymphoma (MZL; n = 4) [43, 48]. Overall response rates (CR + unconfirmed CR + PR) were FL, 60%; MCL, 56%; SLL, 20%; and MZL, 100%. Results show that bortezomib has activity in lymphoma and suggest that sensitivity to bortezomib varies among NHL subtypes.

A summary of phase II clinical trials of bortezomib in the treatment of MCL and FL is shown in Table 2 [43, 49–52]. As evidenced by the results, bortezomib shows activity in these malignancies, and continued study is warranted.

Bortezomib activity is also being studied in solid tumors. Preclinical studies have shown bortezomib to reverse tumor necrosis factor (TNF)-related apoptosis-inducing ligand resistance in human bladder and prostate cancer cell lines [53]. Bortezomib-mediated inhibition of cell proliferation correlated with the nuclear expression of phosphorylated NF-κB and p53 in three breast cancer cell lines [54]. A study in seven different human pancreatic, prostate, lung, and breast cancer cell lines demonstrated that bortezomib-mediated apoptosis correlated with inhibition of NF-κB and reduction in Bcl-2 levels [55]. Clinical trials are in progress to assess the efficacy of bortezomib in treating various solid tumors, including pancreatic, advanced lung, and prostate cancers. A recent phase II trial reported a response rate of 10% for patients with advanced non-small cell lung cancer treated with bortezomib monotherapy and 15.6% when bortezomib was combined with docetaxel [56]. Optimal results with bortezomib in solid tumors will most likely be obtained with combination protocols.

**Toxicity of Bortezomib**

The toxicity profile of bortezomib in clinical trials has been predictable and consistent, with peripheral neuropathy (PN) and thrombocytopenia considered the most clinically important adverse effects [17–19]. These toxicities are manageable with dose reduction and are usually reversible when bortezomib treatment is dose-reduced or discontinued.

The frequency, characteristics, and reversibility of PN were analyzed in patients who received bortezomib (n = 331) in the phase III APEX trial [19, 57]. Peripheral neuropathy (most classified as sensory or not specified; motor neuropathies were rare) developed in 36% of patients, including 9% with grade 3 or 4 PN. Of 91 patients with PN categorized as grade 2 or greater, 68 had bortezomib dose modification according to protocol (reduced dose, n = 37; discontinuation, n = 31), and 23 did not follow the dose-modification protocol. Overall, 64% of the 91 patients with grade 2 or greater PN improved (9%) or had complete resolution (55%) of symptoms. For the 37 patients who received reduced-dose bortezomib, PN improved in 70% to complete resolution to baseline (median time, 78 days). Peripheral neuropathy rates were similar regardless of patient age or the number or type of prior therapies. Peripheral neuropathy was reversible in most patients, and dose modification did not compromise treatment efficacy.

Hematologic adverse events in patients in the phase III APEX trial who received bortezomib (n = 331) or dexamethasone (n = 332) have been analyzed [19, 58]. Thrombocytopenia grade 3 or 4 occurred in 30% of patients who received bortezomib and 7% of patients who received dexamethasone. Bortezomib-associated thrombocytopenia was transient and cyclical, with recovery toward baseline during the rest period of each cycle.
Mechanism of Action
Tipifarnib is a specific inhibitor of farnesyltransferase, an enzyme that mediates post-translational farnesylation of multiple protein substrates involved in tumor cell proliferation, including Ras proteins (Fig. 2). Inhibition of Ras farnesylation does not account for all the effects of farnesyltransferase inhibitors (FTIs). FTIs have been shown to inhibit the activation of a variety of farnesylated proteins involved in signal transduction, tumor cell proliferation, and anchorage-independent growth (e.g., Rho, lamin, centromere-associated protein, protein tyrosine phosphatases, and transforming growth factor β) and have demonstrated antiproliferative activity and indirect antiangiogenic and proapoptotic effects in tumor cell lines [59–62]. Post-translational farnesylation seems to be necessary for the activation of key regulatory proteins, and farnesyltransferase may therefore be a potential target for FTIs across a broad range of malignancies [60].

Clinical Trials
Orally available tipifarnib has demonstrated antiproliferative, antiangiogenic, and proapoptotic activity in vitro and in tumor-bearing animal models, and significant single-agent activity and excellent tolerability in patients with advanced hematologic malignancies. Tipifarnib has been evaluated in clinical studies for the treatment of high-risk acute leukemias and myelodysplastic syndromes (MDS). In a phase I study, patients with high-risk acute leukemias (acute myeloid leukemia [AML], n = 25; chronic myeloid leukemia, n = 3) received escalating doses of 100–1,200 mg of oral tipifarnib twice daily for 21 days every 4 weeks [63]. Overall response rate in this poor-prognosis population was 29%; tipifarnib was well tolerated up to doses of 600 mg twice daily.

A phase II trial (N = 171) evaluated tipifarnib in elderly, previously untreated, poor-risk patients (age >65 years; presence of adverse cytogenetics; secondary AML) with hematologic malignancies who refused or were unfit for conventional induction chemotherapy and may have received palliative treatment or supportive care only [64, 65]. Of the total patient population, 136 (80%) were considered poor-risk; median age was 73 years (range, 34–85 years) with 77 patients (45%) over 75 years of age. An unfavorable karyotype was present in 43% of patients. Patients received oral tipifarnib 600 mg twice daily for 21 days,
followed by a 1–3 week recovery period; patients who achieved CR could receive up to four cycles of tipifarnib. Response was defined as CR (<5% bone marrow myeloblasts, absolute neutrophil count [ANC]) $\geq$ 1,000/$\mu$L, and platelet count $\geq$ 100,000/$\mu$L); PR (similar to CR, except with 5%–19% blasts and a $\geq$ 50% decrease in blasts from baseline); hematologic improvements (HI; similar to PR, except with recovery of ANC to 500–1,000/$\mu$L and platelet count to 20,000–100,000/$\mu$L); and stable disease (anything other than CR, PR, HI, or progressive disease). Response in poor-risk AML was CR in 15%, with an ORR (CR + PR) in 34%; an ORR of 30% was achieved in patients 75 years of age and older. Complete response was associated with prolonged survival; median survival was 433 days for 20 patients who achieved CR and 136 days for the nonresponders. Estimated 12-month survival rate for complete responders was 68%. Disease control (PR, HI, and stable disease) appeared to be associated with a survival advantage; other factors associated with survival advantage were morphologic response (i.e., leukemia-free state) and reduction in tumor burden. The incidence of grade 3 tipifarnib-related nonhematologic adverse events was 43%, and events were mainly infectious and gastrointestinal complications.

In a phase II multicenter study, tipifarnib was evaluated in patients with high-risk MDS; 82 patients, of whom 63% were not treated previously, were enrolled [66, 67]. Patients received 300 mg of tipifarnib twice daily for the first 21 days on a 28-day cycle. Patients were treated for a median of three cycles with overall 72% relative dose intensity. Responses were noted in 34% of patients (seven CR, four CRs with incomplete platelet recovery, and two PR). Median response duration was 10.1 months for patients attaining at least a PR. Myelosuppression was the most common drug-related adverse event (20% grade 3–4 neutropenia; 34% grade 3–4 thrombocytopenia). Nonhematologic adverse events were mainly grade 1–2; adverse events occurring in greater than 10% of patients were fatigue (32%), nausea (26%), diarrhea (20%), rash (11%), and purpura (10%).

Alsina et al. [68] investigated tipifarnib in a phase II trial in patients with advanced multiple myeloma. Tipifarnib 300 mg was administered orally twice daily for 3 weeks every 4 weeks to 43 patients (median age, 62 years; median chemotherapy regimens before study entry, 4). Disease was stabilized in 64% of patients. Tipifarnib suppressed farnesyltransferase in bone marrow and peripheral-blood mononuclear cells and inhibited the farnesylation of HDJ-2, an exclusively farnesylated protein, in unFractionated mononuclear cells and purified myeloma cells. Inhibition of farnesylation did not correlate with disease stabilization. The most common toxicity was fatigue, which occurred in 66% of patients; other toxicities included diarrhea, nausea, neuropathy, anemia, and thrombocytopenia.

The clinical efficacy of tipifarnib is also being investigated in solid tumors, specifically in patients with breast cancer, in combination with taxanes or endocrine therapy [69]. Future studies will determine which solid tumors respond to tipifarnib; a number of clinical trials evaluating tipifarnib combination regimens for solid tumors are in progress [70].

**SUMMARY**

The treatment of cancer continues to evolve and progress as the pathogenesis of the disease is elucidated and new treatment regimens are developed. Among the most exciting new developments is targeted therapy, which specifically attacks the malignancy, resulting in improved efficacy and overall safety. Targeted approaches underscore an important shift in the treatment paradigm for multiple myeloma and other hematologic malignancies that has occurred in recent years, namely a shift away from empirical chemotherapeutic regimens with significant side effects and toward rational, targeted, effective therapies with improved tolerability.

Bortezomib is one of the newest agents for targeted therapy, developed to specifically inhibit the proteasome, leading to increased apoptosis, effects on regulatory proteins, and downregulation of IL-6-triggered signaling cascades. Clinical trials have established the efficacy of bortezomib in the treatment of multiple myeloma. Because other tumors may respond to proteasome inhibition, bortezomib is being evaluated in the treatment of various hematologic and solid malignancies. Continued studies will define the optimal drug combinations and protocols for bortezomib in patients with particular disease characteristics, as well as optimal dosing and scheduling.

Tipifarnib, another targeted agent, inhibits farnesyltransferase, resulting in antiproliferative, antiangiogenic, and proapoptotic activity. Tipifarnib has shown promise in the treatment of AML and MDS, especially in the elderly, in whom these diseases pose a major therapeutic challenge. Tipifarnib is also under investigation for efficacy in solid tumors, specifically for breast cancer in combination with taxane or endocrine therapy. Additional studies, including a prospective randomized trial currently in progress, will need to solidly establish the therapeutic value of tipifarnib.

Bortezomib and tipifarnib are only two new approaches to targeted, more effective, and better tolerated treatment for hematologic cancers. Clinical trials with these agents, as well as the IMiDs, will continue to expand our knowledge and optimize management of patients with hematologic malignancies.
ACKNOWLEDGMENT
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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
J.-P.A., J.D., J.-L.H., and J.S.M. acted as consultants to Ortho-Biotech/Janssen-Cilag within the last 2 years. J.S.M. served as an officer or member of the Board of Ortho-Biotech/Janssen-Cilag within the last 2 years. J.-L.H. has performed contract work for Ortho-Biotech/Janssen-Cilag within the last 2 years.

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