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Bortezomib: clinical profile in lymphoproliferative malignancies

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Abstract

In addition to its efficacy in the treatment of multiple myeloma, the proteasome inhibitor bortezomib appears to be active against a variety of other haematological malignancies. In a phase II trial, bortezomib, given twice weekly for 2 weeks of a 3 week cycle to patients with relapsed, refractory or untreated indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL), produced durable responses in 2/7 MCL patients and stable disease in five. Six of eight patients with follicular NHL achieved a durable response (1 CR, 5 PR). In another study, bortezomib was administered to patients with relapsed or refractory indolent or aggressive B-cell lymphoma. Durable responses were seen in 7/12 MCL patients, including three CR. This apparent activity in MCL is particularly encouraging, given its poor prognosis. These early trial results demonstrate that further clinical testing of bortezomib and additional exploration of the multiple biologic effects of proteasome inhibition are warranted in lymphoproliferative malignancies.

Keywords: Proteasome; Bortezomib; Indolent lymphoma; Mantle cell lymphoma

1. Introduction

In addition to the positive results already obtained in the treatment of multiple myeloma [1], preclinical and early clinical data indicate that the proteasome inhibitor bortezomib may be active against a variety of other haematological malignancies. The proteasome regulates the activity of many proteins involved in cell growth and apoptosis, including nuclear factor-κB (NF-κB). The survival of cell lines from patients with diffuse large B-cell lymphomas has been shown to depend on constitutive NF-κB expression [2,3]. Inhibition of constitutive NF-κB activity by bortezomib in mantle cell lymphoma leads to induction of cell cycle arrest and apoptosis [4]. Proteasome inhibition also induces rapid and extensive apoptosis of leukaemic cells, but leaves normal haematopoietic stem cells viable [5,6].

Preliminary evidence of the activity of bortezomib against non-Hodgkin's lymphoma (NHL) was demonstrated in a phase I study in patients with haematological malignancies. One patient with mantle cell lymphoma and one with follicular lymphoma attained partial remission [7].

In a phase II study in patients with relapsed or refractory indolent lymphomas, 14 patients (accrual on the trial is ongoing and will be updated accordingly) were treated with bortezomib at a dose of 1.5 mg/m^2 twice weekly for 2 weeks with a 1-week rest period [8]. Re-staging studies were performed after two complete cycles of therapy. Of seven patients with follicular lymphoma, one achieved a complete remission (CR) and two achieved a partial remission (PR); two of two patients with small lymphocytic lymphoma achieved only stable disease; and three of five patients with mantle cell lymphoma achieved a PR after two cycles of treatment. The results of this trial support the clinical activity of bortezomib in patients with a variety of NHL subtypes.

Preliminary results from another phase II study of bortezomib in patients with relapsed or refractory indolent and aggressive B-cell lymphomas are also encouraging [9]. Investigators from the M.D. Anderson Cancer Center in Houston, Texas, have reported on 11 patients treated with bortezomib at a dose of 1.5 mg/m^2

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twice weekly for 2 weeks with a 1-week rest period. Of seven evaluable patients with mantle cell lymphoma, five responses were observed, including one CR and two PRs; these met the formal criteria for response. One patient with follicular lymphoma had stable disease. Principal toxicities included grade 3 and 4 gastrointestinal toxicity (nausea, vomiting and/or diarrhoea), thrombocytopaenia, and hypotension. Based on the collective experience in NHL, further clinical evaluation of bortezomib is ongoing.

A number of other clinical trials to assess the efficacy and safety of bortezomib in patients with other haematological malignancies are currently underway. Bortezomib is being evaluated for the treatment of Waldenström's macroglobulinaemia, myelodysplastic syndrome, acute myelogenous leukaemia, and chronic myelogenous leukaemia. Given the potentially important role of the proteasome pathway in the regulation of haematological tumour cell growth and survival, the results of these studies are awaited with interest.

2. Indolent non-Hodgkin's lymphoma and mantle cell lymphoma: the need for new therapeutic strategies

The NHLs are at present the fifth most common cause of cancer-related death in the United States. Collectively, they account for approximately 4–5% of all cancer-related deaths in Caucasian and Hispanic populations and about 2% in African–American populations. However, because some forms of NHL tend to afflict a younger population, the years of life lost is greater than in most other malignancies. This ranks NHL fourth among all cancers with regard to their economic impact in the United States. This year, it is estimated there will be approximately 53,600 new cases of NHL, with over 23,800 deaths attributed to the disease. Thus, the case-fatality rate for NHL (i.e. the number of deaths attributed to the disease/the incidence of the disease) is approximately 44%. As with most haematological malignancies, there is a slight male predominance, with about 57% of all cases developing in males.

The low-grade NHLs comprise approximately one-third of all NHLs. Low-grade lymphoproliferative disorders (including chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL), the follicular lymphomas, marginal zone lymphomas, and lymphoplasmacytoid lymphoma (i.e. Waldenström's macroglobulinaemia)) represent a class of diseases that are characterized by slow progressive tumour growth that responds to conventional cytotoxic therapies, in particular alkylating agents. While complete and partial remissions can be obtained in most patients, over time the disease becomes increasingly more refractory to chemotherapy. A variety of treatment modalities are used to treat low-grade lymphomas. Patients with early-stage disease may be treated initially with localized external beam radiation, which may be curative in some small fraction of patients. Unfortunately, more than 90% of patients present with more disseminated disease and cannot be cured by currently available treatment modalities. The response rates in newly diagnosed patients treated with chemotherapy range from 60% to 80%, while the median duration of response is approximately 2–3 years. Treatment of recurrent or unresponsive disease can vary considerably and can involve the administration of alkylator-based treatments like R-CVP/R-CHOP and chlorambucil, purine-analogue-based therapy with fludarabine, or biologically based therapies with rituximab, interferon, or radioimmunotherapy. In patients with low-grade NHL, the response rate and the duration of response substantially decrease with each sequential course of chemotherapy. Hence, there is a need to identify new agents that are either non-cross-resistant with these prior conventional therapies or that potentially synergize effectively with the existing treatments.

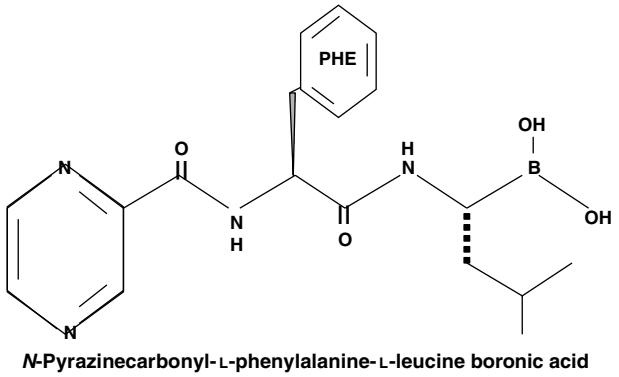
Mantle cell lymphoma is a considerably more difficult disease to treat. Overall, the median survival is in the range of 3–4 years, with a median duration of response of only about 18 months. Typically, the duration of response to subsequent lines of therapy shorten by about 50% with each new line of therapy. While there is no standard of care for patients with this incurable lymphoma, conventional chemotherapy programs like R-CHOP typically produce response rates of about 40–45%, with some more aggressive regimens like HyperCVAD achieving higher complete response rates. The addition of an anthracycline has been shown to improve the number of CRs, and achieving a CR is associated with a longer overall survival. While major remissions can be seen with standard CHOP like chemotherapy programs, the major clinical obstacle remains the durability of response. Mantle cell lymphoma is characterized by a gradually increasing pattern of relapse with successive treatment programs, regardless of the chemotherapy.

Biologically, the molecular changes described in CLL and SLL are heterogeneous. Rearrangements involving a number of different chromosomal sites and oncogenes, including *bcl*-1, *bcl*-2, and *bcl*-3, in addition to deletions, additions, and translocations of chromosomes 11, 12, 13, 14 and 16 have been described in both CLL and SLL. Although originally noted in B-cell CLL, *bcl* -1 rearrangements have been found in only a minority of patients with CLL or SLL, but are commonly found in mantle cell lymphomas (an aggressive chemoresistant lymphoma). In contrast, rearrangements of the *bcl*-2 proto-oncogene are characteristic of follicular lymphomas and exist in about 20% of diffuse large cell lymphomas, while over-expression of bcl-2 is commonly observed in CLL cells. Although proteasome inhibition

has been shown to activate apoptosis in primary human CLL cells *in vitro* (which are 10–20 times more sensitive than normal human lymphocytes), there is a strong biological rationale to assess the clinical activity of proteasome inhibition in other indolent lymphoproliferative disorders where bcl-2 over-expression is well characterized. Pharmacological manipulations that can potentially override the cytoprotective effects of bcl-2 over-expression may afford new opportunities for treating these otherwise incurable diseases.

3. The ubiquitin–proteasome pathway: a novel anticancer target

The major pathway for the degradation of intracellular protein in eukaryotes is the ubiquitin–proteasome pathway [10]. The workhorse of the pathway is the 26S proteasome, an ATP-dependent, multi-catalytic protease. Fig. 1 depicts a schematic of this pathway. Target cytosolic proteins are recognized by a ubiquitin-enzyme complex, which binds to the N-terminus of the protein. In an ATP-dependent reaction, the enzyme complex catalyses the ubiquitination of the ϵ-amino moieties of internal lysine residues. This ubiquitin molecule (a 76 amino acid protein) functions as a tag that is recognised by the 19S regulatory subunit, which when complexed with the 20S proteolytic core, forms the 26S proteasome. Once the target protein is recognised by the regulatory subunit, allosteric changes facilitate the internalisation of the protein into the cylindrically shaped proteasome, bringing it into close proximity with the internal proteases. Once the protein is cleaved, it is discharged through the opposite end. This pathway plays a vital role in degrading regulatory proteins that govern cell cycle control, transcription factor activation, apoptosis, and cell trafficking, including p53, p21, p27, NF-κB, and bcl-2 [10–13]. Preclinical observations have suggested that inhibitors of the ubiquitin–proteasome pathway, agents like lactacystin and the calpain inhibitor ALLN and ALLM, and bortezomib can act through multiple mechanisms to arrest tumour growth, tumour spread, and angiogenesis [5,6,14,15]. Phase I trials have confirmed tolerability of the drug and have suggested possible clinical activity [7,16].



***N*-Pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid**
(PS-341; Bortezomib; Velcade)

Fig. 1.

The ubiquitin–proteasome pathway is essential for transcriptional regulation. Nuclear factor-κB (NF-κB) is a key transcription factor that is responsible for the activation of genes that promote cell proliferation, cytokine release, anti-apoptosis, and changes in cell surface adhesion molecules. NF-κB is tightly regulated by the ubiquitin–proteasome pathway through the accumulation or degradation of IκB, which binds to and inactivates NF-κB [13,17]. Cell adhesion molecules (CAM) such as E-selectin, ICAM-1, and VCAM-1 are a set of proteins regulated by NF-κB and are involved in tumour metastasis and angiogenesis *in vivo* [18]. During metastasis, these molecules direct the adhesion and extravasation of tumour cells to and from the vasculature. As such, tumour cell metastasis may well be contained by the down-regulation of NF-κB-dependent cell adhesion molecule expression. NF-κB is also required by many cells to maintain cell viability as an anti-apoptotic controlling factor [19]. Numerous lines of data now suggest that inhibiting NF-κB activation by stabilising the IκB protein makes cells more sensitive to environmental stress, including chemotherapeutic drugs, ultimately leading to programmed cell death.

Pre-clinical and clinical studies suggest that inhibitors of the ubiquitin–proteasome pathway are a novel and effective means of inducing apoptosis and arresting tumour growth, tumour spread, and angiogenesis. Drugs that can pre-empt the activation of genes capable of inducing various survival signals offer a novel way to intervene in tumour progression.

4. What is bortezomib?

Bortezomib (*N*-pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid, trade name VELCADE, formerly known as PS-341 [CAS # 179324-69-7]) was supplied by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. The chemical structure is presented in Fig. 2. Bortezomib is a dipeptidyl boronic acid inhibitor with high specificity for the 26S proteasome [20]. It is the first member of a new class of anti-tumour agents to come to human trials. Several phase I/II clinical studies have demonstrated that bortezomib is a well-tolerated agent with a short-lived thrombocytopaenia as the major dose-limiting toxicity. In addition, it has been shown that bortezomib is capable of producing a dose-related effect on proteasome inhibition when analysed 1-h post infusion with little inter-patient

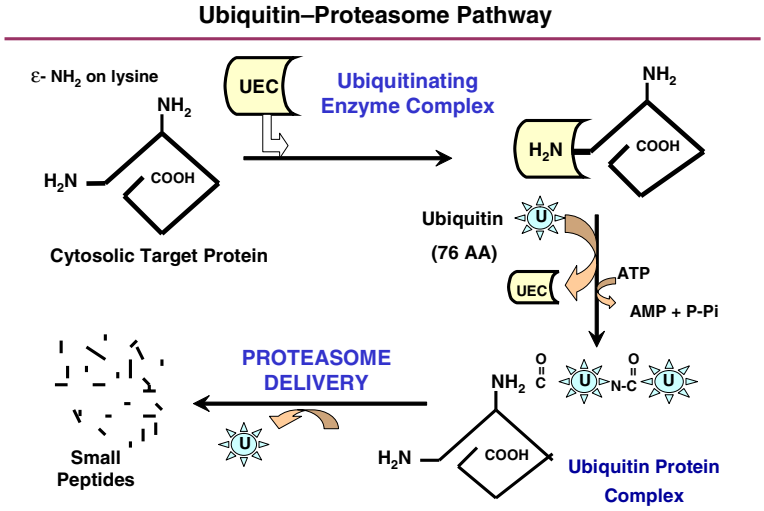


Fig. 2.

variability, with responses at the lowest doses studied to date [7]. Recently, bortezomib was approved by the US Food and Drug Administration for the treatment of relapsed or refractory multiple myeloma, and was also recently recommended for approval in Europe for patients with multiple myeloma who have received at least two prior therapies.

5. The MSKCC phase II experience

This study is a single-center, single-agent phase II study of bortezomib in patients with relapsed, refractory or untreated indolent NHL and mantle cell lymphoma. The major objectives of the study were to determine the frequency and duration of complete and partial response rates for patients with indolent lymphoproliferative disorders treated with bortezomib.

Table 1 presents some of the characteristics of these patients; Table 2 presents toxicity data; and Table 3 shows the early response data. Patients were required to have histologically confirmed lymphoma using the REAL classification, including: chronic lymphocytic leukaemia; B-cell small lymphocytic lymphoma; any marginal zone lymphoma; follicle center cell lymphoma, grades 1, 2, or 3; mantle cell lymphoma and Waldenström's macroglobulinaemia. Patients with transformed lymphoma were allowed as long as they received appropriate chemotherapy for their aggressive disease in the past and on subsequent biopsies had no evidence of aggressive lymphoma. To be eligible for enrollment, patients had to meet the usual criteria, including the following: (1) have measurable disease defined by NCI

Table 1
Patient demographics

Total number of patients	21
Disease	
Follicular	9 (43%)
Mantle cell lymphoma	8 (38%)
Marginal zone lymphoma	1 (5%)
Small/Chronic lymphocytic lymphoma	3 (14%)
Median baseline Karnofsky status (range)	90% (80–90%)
Median age (range)	63 (44–78)
Gender	50% M / 50% F
Average number of prior therapies	2

Table 2
Major toxicities

Total number of patients	
Thrombocytopaenia	Grade 1 = 6 (30%)
	Grade 2 = 6 (30%)
	Grade 3 = 2 (10%)
	Grade 2 = 1 (5%)
Sensory neuropathy	Grade 3 = 1 (5%)
Motor neuropathy	Grade 2 = 1 (5%)
	Grade 3 = 1 (5%)
Small vessel necrotizing vasculitis (new)	Grade 2 = 2 (10%)
Lymphopaenia	Grade 3 = 5 (25%)

Table 3
Patient Response Data

Disease[a]	Response	% Reduction in Tumour Volume	Duration (months)
Follicular NHL	CR = 1	100	6 +
	PR = 5	50–60	3–12 +
(8/9 evaluable)	SD = 1	–	2–6
	POD = 1	–	–
Mantle cell NHL	PR = 2	54–80	6–17
	SD = 5	0–35	3–6 +
(7/8 evaluable)			
SLL/CLL	SD = 2	–	3–6 +
(2/3 evaluable)			

[a] One patient with marginal zone lymphoma.

Sponsored International Working Group [21]; (2) have received no more than three prior regimens of conventional cytotoxic therapy and be off all cytotoxic chemotherapy for at least 4 weeks prior to study enrollment; (3) have a period of at least 3 months since the last administration of any monoclonal antibody; (4) be 18 years of age or older and sign informed consent; (5) have a life expectancy of 3 months or greater; (6) have a Karnofsky performance status >60%; (7) have no sign of congestive heart failure according the New York Heart Failure Guidelines Class III/IV.

In addition, patients were required to meet the following criteria within 2 days of study drug administration: an absolute neutrophil count >1500/μL (if known lymphomatous involvement of the bone marrow, then >500/mL); a platelet count of $\geqslant$ 50,000/μL for the first dose of every cycle and >30,000 for doses delivered on days 4, 8 and 11; a total bilirubin <1.5 times upper institutional limit; an AST(SGOT)/ALT(SGPT) $\leqslant$2.5 times institutional upper limit of normal (4× if liver involvement); and a creatinine <1.5× upper institutional limits. Patients were excluded if they were pregnant; had evidence of intracranial disease; had major surgery within 4 weeks of study drug administration; or had uncontrolled illness including active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, a myocardial infarction or cerebrovascular accident within 6 months of study enrollment, known HIV disease or psychiatric illness/social situations that would limit compliance with study requirements.

Patients were treated twice weekly for 2 weeks (days 1, 4, 8 and 11) followed by a 1-week rest period (one cycle). Patients who failed to meet the eligibility criteria for re-treatment simply missed that dose and resumed treatment once their haematological counts met the stated criteria. Management of the patients' anti-emetic regimen, secondary anemia and neutropaenia were based on standard institutional guidelines.

Response criteria for patients enrolled on study followed the guidelines previously reported by Cheson *et al.* [21]. To date, 21 patients have been registered for the study. Of the 21 patients, a broad panoply of different indolent lymphomas, including 9 patients (43%) who had follicular lymphoma, representing all possible grades, 8 patients (38%) with mantle cell lymphoma, 3 patients with SLL and 1 patient with marginal zone lymphoma. The median number of prior therapies for all patients was two, with nearly 63% of all patients having received at least one course of rituximab and most receiving multiple courses of the antibody. The overwhelming majority of patients had received prior alkylator-based treatment, primarily CHOP or CVP-based chemotherapy with or without rituximab. Only about 10% of patients received prior purine analogue-based therapy, while two had received prior radioimmunotherapy or peripheral blood stem cell transplant. Overall, the drug was very well tolerated. The major toxicity that we already know to be the practical dose-limiting toxicity was thrombocytopaenia, though only two of the 21 patients experienced a grade 3 thrombocytopaenia. Typically, the platelet nadir seen in patients receiving bortezomib is not very deep and is usually very short-lived. Based upon this, the protocol was recently amended to reduce the platelet count from 100,000 to 50,000 for the first dose of any given cycle, and 30,000 for doses 2–4. Neuropathy was mostly grade 1, and in all cases it resolved to baseline grade during the rest week. One patient did develop a grade 2 sensory neuropathy, and one patient developed a grade 3 sensory neuropathy. This latter patient, however, went on to develop a grade 3 sensorimotor neuropathy. Clinically, this patient was strongly suspected of having leptomeningeal disease, but following an aggressive work-up including MRI, lumbar punctures, and EMGs, no organic basis for her neuropathy could be identified.

In addition to these toxicities, we also discovered several patients who developed a vasculitic, like rash, typically during the second cycle after the third or fourth doses. Punch biopsy of some of these patients has confirmed a small vessel necrotising vasculitis. This rash is inconsequential, has never required steroids, an is self-limiting. The most common grade 3 toxicity was in fact lymphopaenia, which is in and of itself and interesting toxicity, given some of the response data in lymphoma we will be discussing below.

To date, we have delivered 62.5 cycles of therapy, of which there were a planned 278 doses, of which 254 were actually delivered. The number of patients who missed at least one dose was about one-third. This was primarily attributed to low platelet counts (i.e. less than 100,000/mL). Since we adjusted the platelet count criteria, the number of reduced doses has fallen dramatically. Other reasons for patients missing doses, though to a much lesser extent, include fatigue and asthaenia. Nine of 21 patients required dose reductions to 1.3 mg/m^2, of which about 4 of these patients required dose reductions to 1.1 mg/m^2, again mostly due to thrombocytopaenia.

The preliminary response data are based on 19 evaluable patients (Table 3). One of the more interesting features of the response data is the dramatic difference seen among the different subtypes of lymphoma. While these are admittedly very small numbers, of 8 evaluable patients with follicular lymphoma, six achieved a major response, including one complete remission and five partial remissions. In all patients achieving a response, the response was confirmed. The patient who achieved the complete remission actually had a duration of response of approximately 9 months, which was longer than that which she had achieved with her prior line of chemotherapy. In the patients with mantle cell lymphoma, seven of the eight patients were evaluable for response. Two have had partial remissions, while the

other five had essentially stable disease. For many of these patients, they remain on active treatment, and it may be too early to determine their overall response as of yet. One of the patients who achieved a partial remission had attained a 6-month duration of remission from CHOP followed by rituximab. After four cycles of therapy, he achieved over an 80% shrinkage of his disease, which has lasted over 19 months. Once his response had exceeded 6 months, we again amended the protocol to allow patients maintaining a durable response to be re-treated. The patient went on to receive a second course of bortezomib, again attaining a second major partial remission that is durable and still in active follow-up 2 months post bortezomib.

Interestingly, no patient with small lymphocytic lymphoma to date has responded, though all have had only stable disease at best. One patient with marginal zone lymphoma just enrolled in the study has demonstrated a PR after only two cycles of bortezomib, though he is still on active treatment.

6. Other experiences with bortezomib in lymphoma

In addition to our study, Dr. Andre Goy at M.D. Anderson Cancer Center in Texas has also been conducting a single-agent, single-institution study of bortezomib in patients with any B-cell neoplasm, regardless of their prior number of treatments. In his presentation at the American Society of Clinical Oncology earlier this year, Dr. Goy reported on 24 patients with a median age of 60 years. Nearly half of the patients he has enrolled to date had mantle cell lymphoma, while the remainder primarily had diffuse large B-cell lymphoma. Overall, his population of patients was more heavily pre-treated, with a median number of prior therapies of 3.2. The overwhelming majority of patients had markedly elevated LDH and β_2-microglobulin prior to study enrollment. Thus far, he has delivered about 52 cycles of therapy, with a mean of 2.1 cycles per patient. Overall, these patients appear to be receiving somewhat less total therapy, which is most likely due to their extensive prior treatment histories. Thus far, four patients have had to discontinue treatment: two secondary to diarrhoea and subsequent hypotension, one due to neuropathy, and one due to thrombocytopaenia. Of note, and though not yet studied in a prospective fashion, Dr. Goy has found that administering 500 to 1000 mL of intravenous normal saline weekly seems to help reduce the asthaenia and fatigue associated with the drug administration.

Of 12 patients with mantle cell lymphoma, seven patients have achieved a major response, three of whom achieved complete remission. In all cases, these responses have been confirmed. Of those patients with diffuse large B-cell lymphoma, only one patient experienced a partial remission, the others all developed progression of disease on study. One patient with SLL had only stable disease on study.

7. Summary

Collectively, the data to date suggest that bortezomib has significant activity in a number of lymphoproliferative malignancies. To date, follicular lymphoma and mantle cell lymphoma appear to be amongst the most responsive diseases to bortezomib. The confirmed activity in mantle cell lymphoma may raise a number of important research opportunities for this disease, especially given its poor prognosis. The ability to achieve durable complete or partial remissions, coupled with the prospect of administering additional cycles of the drug upon relapse, may offer a unique therapeutic strategy that may improve the durability of response to a single agent. It also raises the interesting idea that in this known poor-risk population of patients, a maintenance-like schedule of bortezomib could afford some additional benefit with regard to the durability of the response.

Another intriguing observation to emerge from both studies pertains to the different response rates among the different sub-types of lymphoma. Why did patients in Dr. Goy's study with refractory diffuse large B-cell lymphoma fail to achieve any response? It has been shown that NF-κB over-expression is a molecular feature that appears to characterize these refractory aggressive lymphomas, and given the ability of bortezomib to interfere with this pathway specifically, it is unclear why these types of lymphomas fail to respond.

What is clear is that there is also a wealth of pre-clinical data that suggest that inhibition of the proteasome potently synergises with numerous other conventional cytotoxic therapies, including cyclophosphamide, vincristine, gemcitabine, and even prednisone. One of the theories belying this interaction revolves around the stress response mediated by NF-κB. For those cells not killed outright by exposure to some conventional cytotoxic agent, say irinotecan for example, those cells that survival tend to be characterized by very high levels of NF-κB, which facilitate cell proliferation and anti-apoptosis, providing a survival advantage for those cells. Co-administration of an agent like bortezomib, which could blunt that NF-κB response, could well compromise the survival response, leading to augmented activity. In fact, many pre-clinical studies have demonstrated this mechanism to be important in drug combination studies of bortezomib. It is clear, however, that much future effort will need to be devoted to understanding the panoply of effects mediated by proteasome inhibition and how these effects are likely to change from tissue to tissue, and cancer to cancer. Bortezomib remains a drug with a single target, but capable of producing a multiplicity of biological effects.

Conflict of interest statement

Dr. O'Connor is a member of Millennium Pharmaceuticals' Speakers Bureau.

Role of the funding source

Millennium Pharmaceuticals' Speakers Bureau is education-related.

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