The indolent lymphomas are considered chronic incurable diseases, save the unusual case of radiated stage I disease. Before the introduction of immunotherapy (rituximab and radioimmunotherapies), a series of data from Stanford and other academic centers have shown that the natural history of these diseases has changed little over several decades (1). In the postimmunotherapy era, new analyses have suggested that the natural history of the disease may be changing favorably, with longer median overall survival (2, 3). These data highlight a major theme in the management of indolent non–Hodgkin’s lymphoma (NHL): new drugs have the potential to prolong survival in select indolent lymphoma subtypes. Some of these advances offer patients the prospect of deferring the potential toxicity associated with combination chemotherapy.

An improved understanding of the mechanisms of lymphomagenesis is yielding new opportunities to manage indolent lymphoma. Small-molecule inhibitors of key regulatory pathways will complement a new arsenal of drugs with the potential to either defer or complement combination chemotherapy. For example, many new small molecules targeting Bcl-2 may directly target the pathognomonic t(14;18) in follicular lymphoma (FL; refs. 4–7). Histone deacetylase inhibitors such as vorinostat and desipramide, while influencing a more diverse number of biological pathways, have shown activity in transformed FL (8). Bortezomib is a first in class proteasome inhibitor with significant single agent activity in patients with FL, and that longer durations of treatment may improve overall response.
that has been recently approved for the treatment of mantle cell lymphoma (MCL), with a relatively consistent overall response rate (ORR) of 30% to 40% across five studies, including two multicenter trials (9–13). What has been intriguing about the drug to date has been its less than consistent pattern of activity across many other subtypes of lymphoma, with established activity in MCL and cutaneous T-cell lymphoma, with little to no demonstrated activity in diffuse large B-cell lymphoma, chronic lymphocytic leukemia (CLL), and Hodgkin Lymphoma. The activity in FL has been a subject of controversy as different groups have reported distinctly different results. In this report, we present the results of a multicenter experience focused on the single-agent activity of bortezomib in patients with FL and other forms of B-cell NHL. These data show that the response rate in FL is dependent on the duration of therapy administered. This duration of treatment in FL distinguishes it from MCL, and may account for differences between studies about the ORR in FL. These data have potentially important practical ramifications for the use and development of bortezomib in patients with FL.

**Patients and Methods**

**Patient selection.** Patients were required to have histologically confirmed lymphoma according to the WHO classification, including the following: CLL; small lymphocytic lymphoma (SLL); marginal zone lymphoma (MZL); MCL; FL grades 1, 2, or 3; and Waldenstrom's macroglobulinemia. Patients with a history of transformed lymphoma were allowed as long as they received appropriate chemotherapy for their aggressive disease, and on subsequent biopsies had no evidence of aggressive lymphoma. The eligibility criteria for enrollment are identical to what has been presented earlier (9). This included an absolute neutrophil count of ≥1,000/μL (if known lymphomatous involvement of the bone marrow, then absolute neutrophil count should be >500/μL); a platelet count of ≥50,000/μL for the first dose of every cycle, and >25,000 for doses delivered on days 4, 8, and 11; a total bilirubin ≤1.5 times upper institutional limit; an aspartate aminotransferase/alanine aminotransferase of ≤2.5 times institutional upper limit of normal (4× upper limit of normal if liver involvement); and a creatinine of ≤1.5× upper institutional limits. Patients were excluded if they were pregnant; had evidence of intracranial disease; had major surgery within 4 wk of study drug administration; 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 mo of study enrollment; had known HIV disease; had or psychiatric illness/social situations that would limit compliance with study requirements. The protocol was reviewed individually at each of the participating institutions, and patients signed Institutional Review Board informed consent.

**Study design.** This was a multicenter (Memorial Sloan- Kettering Cancer Center, University of Nebraska, Northwestern University, and Case Western Reserve), single-agent phase II trial of bortezomib in patients with relapsed, refractory, or untreated indolent NHL. The major objectives of the study were to determine the frequency and duration of complete (CR) and partial response (PR) for patients with indolent lymphoproliferative disorders. Patients with MCL were accrued in a separate cohort reported in detail elsewhere (9).

**Drug administration.** Bortezomib was supplied by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Bortezomib for injection was supplied as a lyophilized powder for reconstitution. Each vial contains 3.5 mg of bortezomib and 35 mg mannitol USP. Each vial is reconstituted with 3.5 mL normal saline (0.9%), such that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. The drug was injected over 3 to 5 s into a side arm of a running i.v. infusion of normal saline at 100 mL/h. At the end of the drug infusion, 10 mL of normal saline were infused to flush the i.v. infusion. There was no upper limit on planned therapy, and patients could continue to receive drug as long as there was evidence of clinical benefit without excess toxicity. All patients were started and maintained on prophylactic doses of acyclovir for up to 3 mo after the study discontinuation.

**Dose modification.** Patients were treated with 1.5 mg/m² doses twice weekly for 2 wk (days 1, 4, 8 and 11) followed by a 1-wk rest period (one cycle). Treatment was delayed for peripheral blood counts that fail to meet the eligibility retreatment criteria. Use of antiemetic drugs and cytokine growth factors were based on standard institutional guidelines.

Patients who developed a grade III or IV nonhematologic toxicity, or a grade IV hematologic toxicity, were dose reduced to 1.3 mg/m², and then to 1.1 mg/m² for a repeat episode of toxicity. Patients who experienced persistent or new grade III or IV nonhematologic toxicity or grade IV hematologic toxicity after reduction to 1.1 mg/m² were removed from study. Treatment was delayed until these
**Table 1. Patient demographics**

<table>
<thead>
<tr>
<th>No. of Patients (n)</th>
<th>77*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>49 (64%)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (36%)</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>71 (92%)</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Black Hispanic</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>65 (38-83)</td>
</tr>
</tbody>
</table>

**Disease**

- FL: 22 (29%)
  - Grade 1: 11 (14%)
  - Grade 2: 8 (10%)
  - Grade 3: 3 (4%)
- Mantle: 40 (52%)
- SLL/CLL: 6 (8%)
- MZL: 8 (10%)
- Waldenström's: 1 (1%)

**Median number of therapies**: 3

**Median number of cytotoxic therapies**: 2

**Median time from diagnosis**: 35 mo (1-267)

**Prior therapies**

- Alkylator-based therapy
  - CHOP/RCHOP/EPOCH: 43 (56%)
  - CEP: 3 (4%)
  - CVP/CTX ± Rituximab: 16 (21%)
  - ICE/RICE: 6 (8%)
  - BACOP/MACOP-B: 2 (6%)
  - HyperCVAD: 5 (6%)
  - Chlorambucil: 1 (1%)
  - HDC + ASCT: 8 (10%)

- Purine analogue–based therapy
  - Fludarabine/CyFlu ± R: 18 (23%)
  - FND: 1 (1%)
  - 2-Chlorodeoxyadenosine (2CDA): 2 (3%)

- Biological/experimental-based treatment
  - Rituximab alone: 52 (67%)
  - Zevalin/bexxar: 10 (13%)
  - PEG IFN/ribavirin: 3 (4%)
  - Experimental agents: 5 (6%)
  - Thalidomide: 3 (4%)

- Radiation therapy: 13 (17%)

**Results**

Table 1 presents the general demographic data for all patients registered. Seventy-seven patients were registered for treatment, of which 69 were assessable for response (i.e., they completed at least two cycles of therapy). Of the eight patients (four FL; four MCL) deemed inevaluable; three had marked progression of disease within cycle 1; two developed grade 3 asthenia and thrombocytopenia, requesting to be removed from study after 3 doses; two could not be retreated due to low platelets (original version of protocol had cutoff of >100 K); and one patient did not have the same pretreatment and posttreatment imaging studies performed (i.e., computed tomography prebortezomib, magnetic resonance imaging post). Twenty-two of these 77 patients were part of our initial preliminary experience. Of these 77 patients, 22 have been presented in an earlier report (9). Sixty-four percent of the population was male, with an unintended bias toward a largely white non-Hispanic population (92%). The median age of 65 years, with a range of 38 to 83 years, approximates the median age for patients with indolent lymphomas.

Nearly one third of the population (29%) had FL, only three of whom had FL grade 3. Patients with MZL represented 10% of the study population, whereas SLL/CLL and Waldenström’s macroglobulinemia represented 8%
and 1% (n = 1) of the population, respectively. Overall, this was a reasonably heavily treated population of patients, with a median time from diagnosis of 35 months (range, 1-267 months). The median number of prior therapies was three, of which the median number of prior cytotoxic conventional chemotherapy regimens was two. Two patients had no prior therapy. Excluding those patients who were untreated, all but one patient received at least one form of an alkylator-based treatment program. Twenty-four patients (31%) received at least one course of a purine analogue. In addition, 8 patients had undergone prior autologous peripheral blood stem cell transplant, and 10 had received prior radioimmunotherapy. Sixty-five percent of patients received at least one course of single-agent rituximab, with four of those patients receiving two courses of single agent rituximab.

Table 2. Hematologic and nonhematologic toxicities occurring in 10% or more of patients receiving bortezomib

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>17 (22%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>12 (16%)</td>
<td>8 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (14%)</td>
<td>8 (10%)</td>
<td>4 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (14%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>13 (17%)</td>
<td>4 (5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (26%)</td>
<td>4 (5%)</td>
<td>4 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (26%)</td>
<td>12 (16%)</td>
<td>4 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (44%)</td>
<td>12 (16%)</td>
<td>6</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>38 (49%)</td>
<td>10 (13%)</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7 (9%)</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>12 (16%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>20 (26%)</td>
<td>6 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>17 (22%)</td>
<td>9 (12%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10 (13%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9 (12%)</td>
<td>0</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>16 (21%)</td>
<td>0</td>
<td>4 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>17 (22%)</td>
<td>16</td>
<td>8 (10%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>3 (4%)</td>
<td>27 (35%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (21%)</td>
<td>5 (6%)</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy pain</td>
<td>6 (8%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy sensory</td>
<td>20 (26%)</td>
<td>5 (6%)</td>
<td>6 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils/gran</td>
<td>15 (19%)</td>
<td>10 (13%)</td>
<td>9 (12%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>23 (30%)</td>
<td>15 (19%)</td>
<td>23 (30%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (8%)</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>23 (30%)</td>
<td>2 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td>14 (18%)</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (13%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Given the importance of neuropathic pain, it was included despite occurring in less than 10% of patients.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Response data for patients receiving bortezomib

<table>
<thead>
<tr>
<th>Disease (n = evaluable/total)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>ORR (%; evaluable)</th>
<th>ORR (ITT)</th>
<th>SD (%)</th>
<th>POD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular (n = 18/22)</td>
<td>4 (22.2%)</td>
<td>5 (28%)</td>
<td>9 (50%)</td>
<td>41%</td>
<td>4 (22)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Mantle cell (n = 36/40)</td>
<td>6 (17%)</td>
<td>12 (33%)</td>
<td>18 (50%)</td>
<td>45%</td>
<td>15 (38%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>SLL/CLL (n = 6/6)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>17%</td>
<td>1 (17)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>MZL/Waldenstrom's (n = 9/9)</td>
<td>0 (0)</td>
<td>3 (33)</td>
<td>3 (33)</td>
<td>33%</td>
<td>4 (44%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Total (n = 69/77)</td>
<td>10 (14%)</td>
<td>21 (30)</td>
<td>31 (45%)</td>
<td>40%</td>
<td>24 (35%)</td>
<td>14 (20)</td>
</tr>
</tbody>
</table>

Abbreviations: ITT, intention to treat basis; SD, stable disease; POD, progression of disease.
Two-hundred thirty-two cycles of bortezomib were administered to 77 patients, which included ~1,000 doses of the drug. The median number of cycles administered was three, with 43% of the patients receiving more than three cycles. Similarly, the median number of doses administered was 12, with 48% of patients receiving more than two total doses of bortezomib.

Eight patients (22%) missed at least one dose of drug, whereas four (11%) missed two, and one missed three doses. Two patients each missed four and five doses. The most common reasons for missed doses included thrombocytopenia, fatigue and asthenia, neuropathy, constipation, and neutropenia. Dose reductions to 1.3 and 1.1 mg/m\(^2\) were invoked mostly for patients with neuropathy, neutropenia, and thrombocytopenia. Twelve of 37 (32%) patients required a dose reduction to 1.3 mg/m\(^2\), whereas 4 patients (11%) required dose reductions to 1.1 mg/m\(^2\). The overwhelming reason for dose reduction was attributed to neuropathy, asthenia, and concerns about cytopenias.

Table 2 presents the major toxicities. Other than lymphopenia and thrombocytopenia, there were no major hematologic toxicities. As noted in several experiences to date, lymphopenia continues to be the singular most common grade 3 or 4 toxicity, occurring in 35% of patients (9, 11). There were no opportunistic infections, including no cases of zoster. Grade 3 or 4 thrombocytopenia was seen in 12 patients (31%). Electrolyte abnormalities, frequently seen in the phase 1 studies, were common among these patients, with many experiencing reversible grade 1 or 2 electrolyte imbalance (17).

Neuropathy was primarily grade 1 or 2, with six patients experiencing grade 3 sensory neuropathy. In one of these cases, the grade 3 neuropathy was irreversible.

Table 3 presents the response data from the 77 registered patients, with 69 of those patients being assessable for response. The ORR was 45%, and 40% on an intention to treat basis. Among 18 patients with FL, 9 (50%) achieved a major response, including 4 CR (12%). More accurate assessments of response among the other indolent B-cell lymphoma subtypes were limited by the small number of patients in each group: three of eight patients with MZL attained a partial remission; one patient with Waldenstrom’s macroglobulinemia had stable disease; and one of six patients with SLL/CLL responded to treatment. The median number of cycles of bortezomib delivered to responding and nonresponding patients was 3.75 and 2, respectively (P = 0.01). Nearly twice more therapy was given to the responding patients.

Response durations ranged from approximately 4 to 40 months (three patients remain in remission at the time of this report: 1 patient with untreated MZL at 48+ months and 2 patients with FL at 67+ and 34+ months). The one patient with MZL has had no prior therapy, whereas the patients with FL had relapsed disease following aggressive combination chemotherapy.

Figure 1 presents the time to treatment response for all patients in our data set treated with bortezomib, including patients with MCL. There is a statistically significant difference between the curves for patients with FL versus the curves for patients with MCL and the entire patient population. The median time to response for patients with FL was 11 to 12 weeks, whereas the median time to response for patients with MCL and all other subtypes of NHL was 4 weeks. Statistically, the difference between the MCL and FL curves was highly significant (P = 0.008). These data are still significant (P = 0.01) when the comparison between MCL and all non-MCL patients is made.
Figures 2 through 3 present the PFS survival curves for the population as a whole, as well as different subpopulations. The overall PFS for the entire patient population was 4.75 months, compared with the 9.8 months seen with the line of prior chemotherapy just before study entry (Fig. 2A). Among all responding patients, the PFS with bortezomib was equivalent to the PFS seen with the line of chemotherapy obtained before study (12.3 months for both), which is identical for the FL subpopulation. Overall, patients entering with refractory disease did worse than patients with relapsed disease, although the difference was borderline significant ($P = 0.06$; Fig. 3).

**Discussion**

Inhibition of the proteasome is an important and novel therapeutic approach for the management of lymphoproliferative malignancies. This activity has been well documented in patients with MCL, based now on five independent studies, including two multicenter studies, all of which have yielded an ORR of between 30% and 40% (9–13). This activity has recently led to the approval of bortezomib for the treatment of MCL by the U.S. Food and Drug Administration. The heterogeneous nature of the lymphoproliferative malignancies makes an assessment in these subtypes difficult, especially considering that most subtypes of indolent NHL have an incidence of 1,000 to 5,000 cases per year in the United States.

The experience with bortezomib in other subtypes of NHL is substantially less robust. To date, only two other single agent phase 2 studies have included patients with other subtypes of NHL that have not been MCL devoted. Goy et al. (11) treated 27 patients with non–MCLs, of
which only 4 attained a response (1 CR, 1 unconfirmed complete remission, and 2 PR). The one unconfirmed complete remission occurred in a patient with FL (n = 5), whereas CR occurred in a patient with SLL and partial remissions occurred in one patient with diffuse large B-cell lymphoma and in one with Waldenstrom's macroglobulinemia. Interestingly, the response in FL occurred only after a protocol amendment allowing more protracted schedules of administration, following earlier protocol versions, which required patients to be removed from study after two cycles if they had no response.

In a second study by Straus et al. (10), 13 patients with FL were treated. Two of the 11 patients responded to therapy (18%), which occurred 3 months after the end of treatment. This study, like the one reported by Goy et al. (11), also removed patients from the study for absence of response after one or two cycles of therapy. These observations raise several interesting possibilities about how bortezomib might be working in patients with FL. The late responses, in fact more than half the responses in our current study, and the one from Straus (10), happened after the discontinuation of the study drug. It is also clear from this study analysis that the duration of time on bortezomib treatment is a critical determinant of response (responding patients received twice as much bortezomib). Coupled with the protracted durations of response seen in select patients, the collective scenario raises the possibility that bortezomib may be functioning as an immunomodulatory agent in these patients.

A recent article by Kukreja et al. (18) suggested that dendritic cells (DC) were equally as sensitive to bortezomib as lymphoma cells, and that the killing of DCs may be contributing some component of the responses seen in FL. Other studies have shown that bortezomib kills immature DCs over more mature DCs, implicating bortezomib as a modulator of immune responses in humans through the inhibition of DC maturation (19). Work by Naujokat et al. (20) has established that the effects of bortezomib on DCs is directly attributed to its ability to inhibit proteasomal chymotrypsin-like peptidase activity, which directly impairs the cell surface expression of CD40, CD86, CD80, and HLA-DR among other proteins. These observations are underscored by recent data showing that the length of survival among patients with FL correlates with the molecular features of nonmalignant immune cells present in the tumor at diagnosis (21). Dave et al. (22) showed that the gene expression signature of the coexisting T cells, macrophages, and DCs predicted the outcome of patients with FL. This is in direct contrast to the experience in mantle cell and diffuse large cell lymphoma, where the gene expression signature of the lymphoma predicts outcome. As the tumor microenvironment plays a critical role in influencing the survival of patients with FL (22), targeting or manipulating these stromal T-cell/DC and FL cell interactions may represent an important therapeutic venue in the management of these diseases.

Although the effects on the stromal microenvironment may be a plausible explanation for the activity of bortezomib in FL, it is also well established that bortezomib induces several other effects on the cell, many of which revolve around Bcl-2 and various survival pathways (23–25). Future directions focused on understanding the merits of bortezomib in the indolent lymphomas will continue to explore how best to combine the agent with other known drugs used for these diseases. Combinations of bortezomib and rituximab are well tolerated and active in both FL and MZL (26). These studies that explored different schedules of bortezomib (weekly versus the conventional day 1, 4, 8, and 11 schedule) have suggested less toxicity on a weekly schedule, with possibly comparable efficacy (27). Future studies in indolent lymphoma are certainly warranted; however, a closer examination of possible immunologic factors correlating with response should be studied more intensively.

Disclosure of Potential Conflicts of Interest

O.A. O’Connor, commercial research grant and honorarium, Millennium Pharmaceutical. The other authors disclosed no potential conflicts of interest.

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References


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Time to Treatment Response in Patients with Follicular Lymphoma Treated with Bortezomib Is Longer Compared with Other Histologic Subtypes

Owen A. O’Connor, Carol Portlock, Craig Moskowitz, et al.


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