Cyclophosphamide and Bortezomib With Prednisone or Dexamethasone for the Treatment of Relapsed and Refractory Multiple Myeloma

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Abstract

Clinical trials of the combination of cyclophosphamide, bortezomib, and steroids in relapsed/refractory myeloma have shown promising results, but there is little information about real-world outcomes. We retrospectively reviewed the results of weekly CyBorP(D) in 96 patients treated off-study. The overall response rate was 69%; median progression-free survival was 16.2 months. Toxicity was mild with low rates of myelosuppression and neuropathy.

Introduction: Cyclophosphamide, bortezomib, and prednisone (CyBorP) is a highly effective, well-tolerated regimen in relapsed/refractory multiple myeloma. CyBorP, originally developed at our center to include weekly bortezomib (Bor) and alternate-day prednisone (P), was recently modified so that weekly dexamethasone (D) replaced prednisone. **Patients and Methods:** To assess the effectiveness and tolerability of CyBorP/D in real-world practice, we identified 96 relapsed/refractory patients who received $\geq$ 1 28-day cycle of CyBorP/D, consisting of cyclophosphamide 300 mg/m^2 (days 1, 8, 15, and 22), Bor 1.0 to 1.5 mg/m^2 (days 1, 8, and 15), and either P 50 to 100 mg on alternate days or D 20 to 40 mg weekly between 2007 and 2013. **Results:** Sixty-six (69%) patients achieved $\geq$ partial response: 16 with clinical complete response and 25 with very good partial response; 22 others had stable disease. Progression-free and overall survival for all patients were 16.2 months (95% confidence interval [CI], 7.7-20.1 months) and 26.3 months (95% CI, 21.6-81.2 months), respectively. Although 26 patients had prior Bor exposure, there was no difference in progression-free or overall survival versus Bor-naive patients. **Conclusion:** Toxicities with CyBorP/D were generally mild and manageable. New onset peripheral neuropathy was seen in 13 cases; 9 of 26 patients with pre-existing peripheral neuropathy developed worsening symptoms. No second primary malignancies were observed.

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Introduction

As recently as 10 years ago, therapeutic options for the treatment of relapsed/refractory multiple myeloma (MM) were limited. Prior to the advent of novel drugs, alkylating agents were the mainstay of treatment, and the combination of oral cyclophosphamide (Cy), given at a dose of 500 mg per week, and prednisone (P)—given at a dose of 50 to 100 mg on alternate days—was a regimen commonly used in Canada for relapsed or refractory disease.[1] A National Cancer Institute of Canada Clinical Trials Group study published in 1987 found the CyP regimen to be effective in patients progressing after oral melphalan and prednisone.[2] More recently, in 2005, we reported an overall remission rate (ORR) of 40% with the CyP regimen, when given for first or second relapse after autologous stem cell transplant (ASCT).[3] This study confirmed the effectiveness of the CyP regimen and highlighted the minimal myelosuppression and low incidence of extramedullary toxicities seen with this combination.[3]

The introduction of bortezomib, a first-in-class proteasome inhibitor, dramatically improved the management of patients with

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relapsed and refractory myeloma. In the initial studies, bortezomib was administered twice per week (days 1, 4, 8, and 11), according to a 21-day cycle.[4,5] In 2005, we initiated a phase I/II study that combined CyP (Cy 300 mg/m^2 every week on days 1,8,15, and 22; P 100 mg every other day) given with increasing doses of bortezomib (CyBorP). At the 2 highest dose levels evaluated, bortezomib was administered once (1.5 mg/m^2 on days 1, 8, and 15) or twice per week (1.3 mg/m^2 on days 1, 4, 8, and 11) on a 28-day schedule; both regimens produced high remission rates.[6] Weekly dosing of bortezomib was evaluated in this study, as one goal was to develop a more convenient, yet still efficacious, bortezomib schedule. Specifically, it was hoped that the continuous administration of weekly oral cyclophosphamide, including on day 22 when bortezomib was omitted, would sustain the anti-myeloma effect during the longer interval without bortezomib. According to the weekly bortezomib schedule evaluated, patients experienced a 2-week break without parenteral treatment between the day 15 dose of bortezomib and the start of the next cycle on day 28, circumventing the need for a clinic visit on day 22. In this study, CyBorP with bortezomib 1.5 mg/m^2 given 3 times per month demonstrated an ORR of 85% and complete remission (CR) plus near CR rate of 54% in patients with relapsed and refractory MM; the 1-year progression-free survival (PFS) for this dose level was 83%.[6]

A subsequent collaborative phase II study conducted at the Scottsdale Mayo Clinic and Princess Margaret Cancer Centre evaluated the efficacy of a similar regimen of weekly bortezomib in 63 newly diagnosed patients with MM. However, in this study, bortezomib was given every week in the 28-day cycle, without a break on day 22. In addition, dexamethasone was utilized instead of prednisone as the corticosteroid (CyBorD).[7] Although the later study was not randomized, it clearly illustrated the comparable efficacy between weekly bortezomib (1.5 mg/m^2) administered in a 28-day cycle and bortezomib (1.3 mg/m^2) given twice per week in a 21-day cycle. In addition, considerably less toxicity was reported with the weekly schedule than with the twice per week schedule, with lower rates of grade $\geq$ 3 thrombocytopenia (0% vs. 21%) and peripheral neuropathy (0% vs. 6%). These favorable results have led to the widespread adoption of CyBorD (with bortezomib given once per week) as the standard induction regimen before ASCT throughout Canada and in other centers. A recently published report of the CyBorD induction regimen before ASCT in 109 patients at the Princess Margaret Cancer Centre confirmed the efficacy of this combination, which was well-tolerated and which produced an ORR of 95%.[8]

Given the results of the above studies, CyBorD has been adopted into clinical practice in the relapsed and refractory setting at our institution. However, the real-world effectiveness of this regimen has not been extensively evaluated in the relapsed/refractory setting and was therefore the focus of this retrospective review of patients treated at the Princess Margaret Cancer Centre.

Patients and Methods

Patients

All relapsed and refractory patients with MM who were treated with at least 1 cycle of weekly CyBorP or CyBorD (CyBorP/D) between January 2007 and November 2013 at the Princess Margaret Cancer Centre were included in this retrospective analysis. Patients were identified and characterized via the Princess Margaret Cancer Centre Multiple Myeloma Database as well as via pharmacy records, with individual chart reviews undertaken as necessary. The study population consisted of both bortezomib-naive patients and those who had been given this agent as part of induction therapy, for example, before ASCT, or as treatment for a previous myeloma relapse.

Treatment Administered

Initially, treatment consisted of a 28-day cycle of oral cyclophosphamide, 300 mg/m^2 on days 1, 8, and 15; bortezomib, 1.5 mg/m^2 on days 1, 8, and 15; and prednisone, 50 mg or 100 mg on alternate days. Cyclophosphamide was commonly given at a flat dose of 500 mg, as per earlier Canadian studies. After publication of the Eastern Cooperative Oncology Group E4A01 study in 2010, which highlighted the improved efficacy and reduced toxicity of weekly dexamethasone versus the 4-day pulse schedule given 3 times per month, most patients received dexamethasone at a weekly dose of 20 mg or 40 mg, rather than prednisone.[9] The choice and dose of corticosteroids was based on patient and physician preference. Also, at the discretion of the physician, some patients received a reduced weekly dose of bortezomib (1.0 mg/m^2 or 1.3 mg/m^2), usually on the basis of pre-existing peripheral neuropathy or, less commonly, pre-existing cytopenias.

When the study first started, patients received intravenous bortezomib; however, after September 2012, subcutaneous injection was adopted as the standard administration method at the Princess Margaret Cancer Centre.[10] Initially, patients were treated with all 3 drugs until disease progression or unacceptable toxicity. However, as of 2012, cyclophosphamide was discontinued after approximately 2 years in the majority of patients achieving at least a VGPR to potentially reduce the risk of late toxicity resulting from this agent, such as second primary malignancies. Bortezomib and steroids, however, were continued until progressive myeloma was documented.

Most patients received antiviral prophylaxis with acyclovir given at a dose of 400 mg twice per day. Other supportive care measures such as blood transfusions, erythropoietin-stimulating agents, and/or granulocyte colony-stimulating factor were used as needed. This retrospective study was approved by the University Health Network Research Ethics Board.

Patient Groups

All patients in this study were treated with CyBorP/D in the setting of relapsed and refractory MM. To further explore the efficacy of this regimen, patients were subdivided into the following 3 groups: bortezomib-naive (Bor-naive), bortezomib-exposed (Bor-exposed), and bortezomib as re-induction therapy for salvage ASCT (Bor-pre-sASCT).

Evaluation of Response

Responses were evaluated according to modified European Group for Blood and Marrow Transplantation criteria, with the inclusion of the category of VGPR defined as a greater or equal to 90% reduction in the serum M-component plus a urine M-component less than 100 mg per day.[11] Moreover, bone marrow aspirates and biopsies were not routinely obtained for response determination in this nonresearch experience; therefore, the term