Modified HyperCVAD Versus Bortezomib-HyperCAD in Patients With Relapsed/Refractory Multiple Myeloma

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Abstract

Despite the availability of novel treatments for multiple myeloma, resistance to chemotherapy inevitably develops. We retrospectively reviewed the outcomes of patients with relapsed and/or refractory disease treated with modified hyperCVAD (n = 15) or bortezomib-hyperCAD (n = 18). Effectiveness and safety outcomes were similar in each group, with the entire cohort of patients showing an overall response rate of 42%.

Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy, in which aggressive relapses might require salvage cytotoxic infusional chemotherapy. Several clinical trials that reported the efficacy of bortezomib led to institutional practice changes in which vincristine was replaced with bortezomib in the modified hyperCVAD regimen, creating a new treatment regimen, named "bortezomib-hyperCAD." **Patients and Methods:** We retrospectively describe the effectiveness and tolerability of 2 chemotherapy regimens among 33 patients with relapsed and/or refractory MM. Patients who received ≥ 1 cycle of modified hyperCVAD or bortezomib-hyperCAD between 2011 and 2015 were assessed. **Results:** The median number of cycles administered in each arm was 2. The overall response rate was 40% (6 partial responses) in the modified hyperCVAD group and 44.4% (1 complete response, 1 very good partial response, and 6 partial responses) in the bortezomib-hyperCAD group (Fisher exact $P = .80$). Median progression-free survival (PFS) and median overall survival (OS) for patients in the modified hyperCVAD group was 6.3 months and 11.1 months, respectively. This was comparable with patients in the bortezomib-hyperCAD group, who had a median PFS of 6.6 months and a median OS of 13.8 months (log rank $P = .54$ and .66, respectively). There was no statistically significant association between treatment arm and febrile neutropenia, emergency department visits, hospitalizations, or peripheral neuropathy (all Fisher exact P values $> .05$). **Conclusion:** Overall effectiveness and tolerability outcomes were similar between modified hyperCVAD and bortezomib-hyperCAD, with both regimens showing an impressive response rate among refractory and heavily pretreated patients with relapsed MM.

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Introduction

Multiple myeloma (MM) is an incurable plasma cell malignancy. Historically, oral alkylating agents and steroids were used as first-line therapy and 50% to 60% of patients achieved at least a partial response (PR). However, median overall survival (OS) remained low at 2 to 3 years.[1] Response rates and OS for patients with MM have improved in the past decade with the incorporation of novel agents, such as proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs), and refinement of autologous stem cell transplantation (ASCT), consolidation, and maintenance strategies.[2,3] Despite these advances, nearly all patients with MM relapse and eventually develop refractory disease. The available options for relapsed/refractory patients include re-treatment with the initial induction agents or newer drugs, including carfilzomib, ixazomib, pomalidomide, panobinostat, elotuzumab, daratumumab, bendamustine, and liposomal doxorubicin.[4-11] However, more aggressive relapses might benefit from salvage cytotoxic infusional chemotherapy.[12]

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In the early 1990s, before the introduction of novel agents, few effective treatments were available for patients with advanced MM resistant to alkylating agents as well as VAD (the combination of vincristine, doxorubicin, and dexamethasone). At the time, several useful regimens[13-15] of high-dose alkylating agents were associated with significant toxicities and therefore restricted to younger patients with few comorbidities. In an effort to develop an effective, but less toxic therapy, Dimopoulos et al examined the role of hyperCVAD in 58 patients (median age, 58 years) with relapsed/refractory MM.[16] The regimen consisted of cyclophosphamide 300 mg/m^2 intravenous (I.V.) every 12 hours for 6 doses on days 1 through 3, vincristine 2 mg and doxorubicin 50 mg/m^2 continuous I.V. infusion over 48 hours starting on day 4, vincristine 2 mg rapid I.V. injection on day 11, and dexamethasone 20 mg/m^2 orally on days 1 through 5 and days 11 through 14. Patients also received mesna and growth factor support. This treatment regimen resulted in a response rate of 40% and a median OS of 15 months.[16]

Our institution adopted this treatment regimen, but with several modifications as described in the *Treatment Administered section*, and thus it was termed "modified hyperCVAD." Subsequently, in 2010, Harousseau et al reported that VD (bortezomib with dexamethasone) improved overall response rate (ORR) compared with VAD, with a similar adverse effect rate.[17] This clinical trial, along with other published studies reporting the efficacy of bortezomib in the relapsed/refractory setting,[18-20] prompted the additional use of bortezomib with modified hyperCVAD, but with the removal of vincristine to avoid the overlapping toxicity of peripheral neuropathy (PN). To our knowledge, this new regimen, named "bortezomib-hyperCAD," has not been formally studied or previously described in the literature.

The focus of this retrospective review was to evaluate the effectiveness and safety of the modified hyperCVAD and bortezomib-hyperCAD regimens among relapsed and/or refractory MM patients treated at the Oregon Health and Science University (OHSU) Knight Cancer Institute.

Patients and Methods

Patients

All relapsed and/or refractory patients with MM who were treated with at least 1 cycle of modified hyperCVAD or bortezomib-hyperCAD between November 2011 and September 2015 at the OHSU Knight Cancer Institute were included in this retrospective analysis. Patients were identified for screening via medication administration records and a manual medical record review was performed. Patients were excluded if they received treatment with modified hyperCVAD as well as bortezomib-hyperCAD, or if cycle 1 of the treatment regimen was modified to omit any of the originally intended chemotherapy agents. The OHSU Institutional Review Board approved this study.

Treatment Administered

A comparison of the modified hyperCVAD and bortezomib-hyperCAD chemotherapy regimens is outlined in Table 1. For most patients, treatment cycles were administered every 4 weeks. However at the discretion of the physician, cycles were given every 3 weeks in cases of early hematopoietic cell recovery, or were delayed in cases of toxicity. In 2011, Moreau et al established that subcutaneous (s.c.) administration of bortezomib results in less PN compared with I.V. administration of the same doses.[21] For this reason, all patients received bortezomib via the s.c. route. At the discretion of the physician, some patients received reduced doses of the chemotherapy agents on the basis of preexisting toxicities, such as PN or cytopenias, or because of tolerability throughout the treatment cycles. All patients received granulocyte colony-stimulating factor (pegfilgrastim) 24 to 48 hours after the completion of chemotherapy, antiviral prophylaxis with acyclovir daily, and mesna 350 mg/m^2/d continuous I.V. infusion every 24 hours on days 1 through 4. Most patients also received antifungal, antibacterial, and *Pneumocystis jiroveci* pneumonia prophylaxis, as well as other supportive care measures, such as blood transfusions. All patients were admitted to the hospital for administration of chemotherapy.

Statistical Analysis

The primary objective was to determine ORR and type of response: complete response (CR), very good PR (VGPR), PR, minimal response (MR), stable disease (SD), or progressive disease (PD) as per the European Society for Blood and Marrow Transplantation (EBMT)/International Myeloma Working Group (IMWG) uniform response criteria.[22-24] Secondary objectives included clinical benefit rate (CBR), number of patients proceeding directly to ASCT (either first or second ASCT), progression-free survival (PFS), OS, and tolerability. Incidence of dose modifications and reasons for treatment discontinuation were also assessed. ORR included patients with PR or better and CBR included patients with SD or better.

Fisher exact test and χ^2 test were used to assess the association between categorical baseline demographic and clinical characteristics, efficacy outcomes, and treatment. The *t* test and Wilcoxon rank sum test were used to compare continuous covariates (age, time from diagnosis to cycle 1, day 1 [C1D1] of treatment, number of previous lines of therapy, and number of cycles) between treatment groups. PFS time was defined as the interval from the date of C1D1 of chemotherapy to the date disease progression was noted. Patients alive without evidence of disease relapse or progression were

Table 1 Comparison of Modified HyperCVAD and Bortezomib-HyperCAD Chemotherapy Regimens

	Modified HyperCVAD	Bortezomib-HyperCAD
Bortezomib	None	1.3 mg/m^2 s.c. on days 1 and 4
Cyclophosphamide	300 mg/m^2 I.V. every 12 hours for 8 doses on days 1 through 4	300 mg/m^2 I.V. every 12 hours for 8 doses on days 1 through 4
Vincristine	0.4 mg/d continuous I.V. infusion every 24 hours on days 1 through 4	None
Doxorubicin	9 mg/m^2/d continuous I.V. infusion every 24 hours on days 1 through 4	9 mg/m^2/d continuous I.V. infusion every 24 hours on days 1 through 4
Dexamethasone	40 mg p.o. every 24 hours on days 1 through 4	40 mg p.o. every 24 hours on days 1 through 4
Pegfilgrastim	6 mg s.c. once on day 5 or 6	6 mg s.c. once on day 5 or 6

Abbreviations: I.V. = intravenous; p.o. = orally; s.c. = subcutaneous.