CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Cyclophosphamide–bortezomib–dexamethasone compared with bortezomib–dexamethasone in transplantation-eligible patients with newly diagnosed multiple myeloma

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ABSTRACT

Introduction Cyclophosphamide–bortezomib–dexamethasone (CyBorD) is considered a standard induction regimen for transplant-eligible patients with newly diagnosed multiple myeloma (MM). It has not been prospectively compared with bortezomib–dexamethasone (Bor-Dex). We aimed to compare the efficacy of CyBorD and Bor-Dex induction in transplant-eligible patients.

Methods In a retrospective observational study at a single tertiary centre, all patients with transplant-eligible MM who received induction with CyBorD or Bor-Dex between March 2008 and April 2016 were enrolled. Progression-free survival (PFS), response, and stem-cell collection for a first autologous stem-cell transplantation (aHSCT) were compared.

Results Of 155 patients enrolled, 78 (50.3%) had received CyBorD, and 77 (49.7%), Bor-Dex. The patients in the Bor-Dex cohort were younger than those in the CyBorD cohort (median: 57 years vs. 62 years; $p = 0.0002$) and more likely to have had treatment held, reduced, or discontinued (26% vs. 14.5%, $p = 0.11$). The stem-cell mobilization regimen for both cohorts was predominantly cyclophosphamide and granulocyte colony–stimulating factor (GCSF). Plerixafor was used more often for the CyBorD cohort ($p = 0.009$), and more collection failures occurred in the CyBorD cohort ($p = 0.08$). In patients receiving Bor-Dex, more cells were collected (9.9×10^6 cells/kg vs. 7.7×10^6cells/kg, $p = 0.007$). At day +100, a very good partial response or better was achieved in 75% of the CyBorD cohort and in 73% of the Bor-Dex cohort ($p = 0.77$). Median PFS was 3.2 years in the Bor-Dex cohort and 3.7 years in the CyBorD cohort ($p = 0.56$).

Conclusions Overall efficacy was similar in our patients receiving CyBorD and Bor-Dex. After aHSCT, no difference in depth of response or PFS was observed. Cyclophosphamide–GCSF seems to increase collection failures and hospitalizations in patients receiving CyBorD. Prospective studies are required to examine that relationship.

Key Words Myeloma, bortezomib, toxicity, CyBorD

Curr Oncol. 2020 April:27(2)e81–e85 www.current-oncology.com

INTRODUCTION

Bortezomib is an effective drug to treat patients with multiple myeloma (MM), and it is currently a standard treatment for newly diagnosed patients. Initially, it was given as a single agent or in combination with dexamethasone (Bor-Dex)[1,2], but after studies showing that 3-drug induction regimens could deepen response rates and improve survival, therapies such as CyBorD (cyclophosphamide–bortezomib–dexamethasone) have been used in many centres, including our own, as first-line remission induction

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before autologous stem-cell transplantation (aHSCT)[3]. Given that bortezomib is not associated with poor peripheral mobilization and collection of hematopoietic stem and progenitor cells (HSPCs), Bor-Dex has been used as the main pillar of 3- or 4-drug regimens[4–6].

Data supporting CyBorD come largely from phase II studies that demonstrated its safety and tolerability[3,6–9]. Those studies also reported impressive overall response rates (ORRs) above 90% after 4 cycles of CyBorD, and no further gain with the addition of a fourth agent (lenalidomide) to the CyBorD regimen[9]. Recently, various bortezomib-containing regimens used as first-line treatment for transplant-ineligible patients with MM were evaluated[10], and ORRs of 95.2%, 80.9%, and 76.3% were observed in patients treated with, respectively, CyBorD, bortezomib–melphalan–prednisone, and Bor-Dex (p = 0.03). Median overall survival (OS) was similar in the three cohorts, but a trend toward better progression-free survival (PFS) was observed with CyBorD.

CyBorD and Bor-Dex have never been compared in a prospective randomized trial. Our retrospective observational study compared tolerability, efficacy, and outcomes for those two commonly used regimens in transplant-eligible patients with newly diagnosed MM.

METHODS

This retrospective observational cohort study enrolled consecutive transplant-eligible patients newly diagnosed with MM between March 2008 and November 2015 who received induction therapy with either CyBorD or Bor-Dex, followed by peripheral HSPC mobilization and collection, and aHSCT at our centre. Data were extracted from electronic medical records and from the blood and marrow transplant database. The local research ethics board approved the study.

The primary outcome was PFS. Secondary outcomes were OS, myeloma response, treatment toxicity during induction therapy, adverse events secondary to HSPC mobilization, and collection yield.

Progression-free survival was defined as time from diagnosis to date of first relapse requiring therapy after aHSCT or to date of death. Overall survival was defined as time from diagnosis to date of death from any cause; patients were censored at their last follow-up.

Response was defined using the International Myeloma Working Group criteria, but because access to serum free light-chain assays was not available during the study period, response was defined by serum (SPEP) and urine protein electrophoresis (UPEP) and by immunofixation electrophoresis alone. Changes in paraprotein were compared at diagnosis and at the last measurement before mobilization chemotherapy (induction response) and at diagnosis and at day +100 after first-line aHSCT. Responses were categorized as follows: complete response (patients with negative serum and urine immunofixation electrophoresis); very good partial response [VGPR (detectable abnormal bands only by immunofixation electrophoresis, or 90%–99% monoclonal peak reduction in SPEP and urinary paraprotein <0.1 g/24 h)]; partial response (50%–89% paraprotein reduction in SPEP and ≥90% drop in UPEP); stable disease (<50% paraprotein reduction in SPEP and <25% paraprotein increase in SPEP, or <90% paraprotein reduction in UPEP); and progressive disease (≥25% paraprotein increase in SPEP or UPEP). We also compared the number of patients achieving ORR and the number achieving a deeper response (≥VGPR).

During induction therapy, treatment toxicity was assessed based on the percentage of dose adjustments in each cohort and on the diagnostic reasons for the readjustments; the number of episodes of fever and pain after receipt of HSPC mobilization agents were used to capture mobilization toxicity.

Treatment

Patients in the Bor-Dex cohort received bortezomib 1.3 mg/m^2 (97% of patients) or 1.5 mg/m^2 (3% of patients) on days 1, 4, 8, and 11 of a 21-day cycle, delivered either intravenously [IV (60% of patients)] or subcutaneously [SC (40% of patients)] according to standard practice at the time of diagnosis, plus oral dexamethasone 40 mg once daily on days 1–4 and 9–12. Patients in the CyBorD cohort received SC bortezomib 1.5 mg/m^2, oral cyclophosphamide 300–500 mg, and oral dexamethasone 40 mg weekly. The cumulative planned dose for 4 cycles of bortezomib was 20.8 mg/m^2 in the Bor-Dex cohort and 24 mg/m^2 in the CyBorD cohort.

Collection of HSPCs aimed to result in 2×10^6 CD34+ cells or more per kilogram, but the decision to proceed with aHSCT with fewer cells was made individually. The HSPC mobilization was attempted using either IV cyclophosphamide 2.5 g/m^2 plus SC granulocyte colony–stimulating factor 10 µg/kg daily (cyclophosphamide–GCSF) or SC plerixafor 0.24 mg/kg plus GCSF 10 µg/kg daily (plerixafor–GCSF). A salvage dose of plerixafor was given to patients if mobilization with cyclophosphamide-GCSF failed. Transplant conditioning regimens used were IV melphalan 200 mg/m^2; IV melphalan 140 mg/m^2; and IV busulfan 3.2 mg/kg daily for 3 days, plus IV melphalan 140 mg/m^2.

Statistical Analysis

Continuous variables are reported as medians with ranges and were compared using the Mann–Whitney test. Categorical variables were compared using the Pearson or chi-square test as appropriate. The Kaplan–Meier method was used to estimate PFS and OS curves that were compared using the log-rank test. Statistical analyses were generated using the GraphPad Prism software application (version 6.00: GraphPad Software, La Jolla, CA, U.S.A.), and significance was accepted at $p < 0.05$.

RESULTS

Patients and Disease Characteristics

The study included 155 patients: 78 in the CyBorD cohort (50.3%), and 77 in the Bor-Dex cohort (49.7%). Patient and disease characteristics in the cohorts were similar (Table I). Median number of induction cycles was 4, with a range of 3–9 cycles in the CyBorD cohort and 2–9 cycles in the Bor-Dex cohort (p = 0.34). The relative proportion of patients treated with CyBorD increased annually: 1 of 67 (1.5%) for those diagnosed until 2012, 20 of 30 (67%) in 2013, 32 of 33 (97%) in 2014, and 25 of 25 (100%) in 2015.

TABLE I Patient and disease characteristics at baseline (diagnosis)

Characteristic	First-line treatment cohort		*p* Value
	Bor-Dex	CyBorD	
Evaluable patients [*n* (%)]	77 (100)	78 (100)	
Age (years)			0.0002
Median	57	62	
Range	35–69	39–72	
Sex [*n* (%) men]	44 (57)	51 (65)	0.29
Myeloma subtype [*n* (%)]			0.23
IgG	42 (54)	51 (65)	
Non-IgG	16 (21)	13 (17)	
Light chain	16 (21)	14 (18)	
Non-secretory	3 (4)	—	
ISS stage [*n* (%)]			0.31
I	21 (27)	13 (16.7)	
II	25 (33)	30 (38.4)	
III	27 (35)	28 (35.9)	

Bor-Dex = bortezomib–dexamethasone; CyBorD = cyclophosphamide–bortezomib–dexamethasone; ISS = International Staging System.

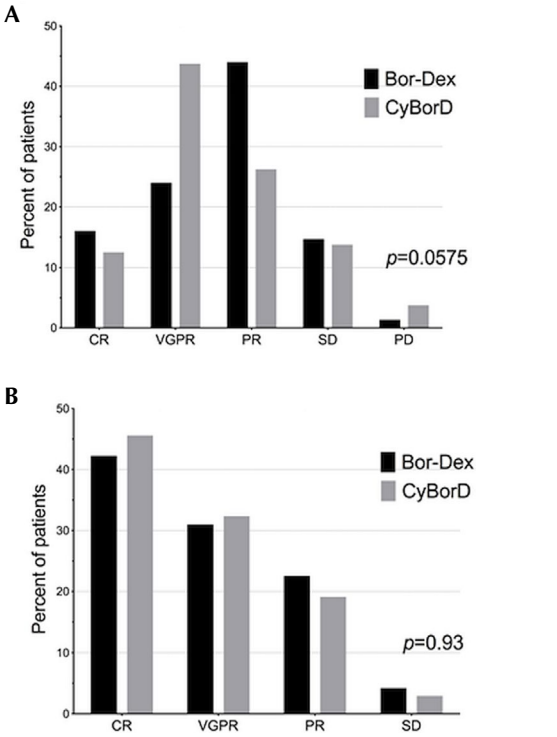

FIGURE 1 Response observed in each cohort (A) after first-line induction and (B) at day +100 after consolidative autologous stem-cell transplantation. The percentages of patients achieving a complete response (CR), a very good partial response (VGPR), a partial response (PR), stable disease (SD), and progressive disease (PD) after each therapy are shown. Bor-Dex = bortezomib–dexamethasone; CyBorD = cyclophosphamide–bortezomib–dexamethasone.

Induction Response and Toxicity

Figure 1 shows the myeloma response to induction. Response was deeper in the CyBorD cohort (≥GPR) than in the Bor-Dex cohort after induction therapy (59% vs. 40%, $p = 0.02$), but the ORR was similar in both cohorts (87% vs. 84%, $p = 0.62$).

Toxicity secondary to induction therapy was assessed using the proportion of patients requiring dose adjustments in each arm. Holds, dose reductions, and dose discontinuations occurred more often in the Bor-Dex cohort than in the CyBorD cohort (26% vs. 14.5%, $p = 0.11$). Peripheral neuropathy was the adverse event most commonly reported during induction by patients in both cohorts, occurring in 35.5% of the Bor-Dex cohort and in 24% of the CyBorD cohort ($p = 0.16$), and it was responsible for 70% of the dose adjustments in the Bor-Dex and CyBorD cohorts, $p > 0.99$. Requirement for hospitalization because of induction side effects was not significantly different in the two cohorts (6.6% with Bor-Dex and 5.5% with CyBorD, $p > 0.99$), with no statistical difference in length of stay (median: 5 days vs. 10 days, $p = 0.34$). All hospital admissions during induction therapy in both cohorts were a result of infection.

HSPC Mobilization and Collection

The mobilization regimens given differed significantly, highlighting the discrepancy in plerixafor use in the two cohorts (Table II). In the CyBorD cohort, more upfront ($n = 6$, 8%) and salvage plerixafor ($n = 4$, 5%) was used, whereas in the Bor-Dex cohort, 1 patient (1%) received planned plerixafor–GCSF because of pre-existing cytopenias.

In the two cohorts, the percentages of adverse events secondary to mobilization with cyclophosphamide–GCSF were similar, but during HSPC mobilization, a trend toward more hospitalizations was observed in the CyBorD cohort compared with the Bor-Dex cohort (24.4% vs. 14%, $p = 0.11$). The main reason for hospital admission secondary to HSPC mobilization was infection in both cohorts: 73% in the Bor-Dex cohort, and 95% in the CyBorD cohort. Other causes of hospitalization included severe bone pain ($n = 1$, 9%) and hyponatremia ($n = 2$, 18%) in the Bor-Dex cohort, and gastrointestinal intolerance ($n = 1$, 5%) in the CyBorD cohort.

Collection of sufficient HSPC for 2 autologous transplants (≥5×10^6 CD34+ cells/kg) was possible in 91% of patients in the Bor-Dex cohort and in 75.6% of patients in the CyBorD cohort ($p = 0.005$).

Transplantation Outcomes

In the present study, all 77 patients (100%) in the Bor-Dex cohort and 74 of the 78 patients (95%) in the CyBorD cohort proceeded to aHSCT. Failure of HSPC collection despite salvage plerixafor affected 3 of the 4 patients (4%) receiving CyBorD who did not proceed, and 1 patient (1%) died from acute renal failure and septic shock before aHSCT admission.

Most patients received IV melphalan 200 mg/m^2 as conditioning (97.4% in the Bor-Dex cohort and 94.6% in the CyBorD cohort). In each cohort, 2 patients received IV melphalan 140 mg/m^2. Another 2 patients in the CyBorD cohort (2.7%) received IV busulfan plus IV melphalan conditioning. The depth of response at day +100 was similar in the patients who had been treated with Bor-Dex and CyBorD (Figure 1), with 73.2% of the Bor-Dex cohort and 75.4% of the CyBorD cohort achieving a VGPR or better ($p = 0.77$).

TABLE II Mobilization of hematopoietic stem and progenitor cells (HSPCs)

Mobilization characteristic	First-line treatment cohort		*p* Value
	Bor-Dex (*n*=77)	CyBorD (*n*=78)	
Mobilization regimen [*n* (%)]			0.009
Cyclophosphamide–GCSF	76 (99)	68 (87)	
Plerixafor	1 (1)	10 (13)	
Failure of HSPC collection [*n* (%)]	—	3 (4)	0.08
Mobilization toxicity [*n* (%)]	27 (35)	28 (36)	0.91
Toxicity diagnosis after mobilization [*n* (%)]			
Febrile neutropenia	11 (14)	16 (21)	0.36
Non-neutropenic fever	2 (3)	5 (6)	0.44
Pain	9 (11.7)	6 (8)	0.40
Admission required after mobilization [*n* (%)]	11 (14)	19 (24.4)	0.11
Days admitted			0.85
Median	3	3	
Range	1–21	1–6	
CD34+ cells collected ($\times 10^6$/kg)			0.007
Median	9.9	7.7	
Range	3.1–28.3	1.9–35.3	
Days of apheresis *(n)*			0.23
Median	1	1	
Range	1–2	1–2	

Bor-Dex = bortezomib–dexamethasone; CyBorD = cyclophosphamide–bortezomib–dexamethasone; GCSF = granulocyte colony–stimulating factor; HSPC = hematopoietic stem and progenitor cell.

Survival

No statistical difference in PFS (Figure 2) was observed between the cohorts, with a median PFS of 3.2 years in the Bor-Dex cohort and 3.7 years in the CyBorD cohort (p = 0.54). Median OS was 7 years after diagnosis in the Bor-Dex cohort and not reached in the CyBorD cohort (p = 0.52).

In the CyBorD cohort, 3 patients died before day +100 after aHSCT (4%), but no deaths occurred before day +100 in the Bor-Dex cohort. The causes of the 3 early deaths (4%) in the CyBorD cohort were septic shock during the aHSCT admission (n = 2, 2.7%) and progressive disease at day +81 (n = 1, 1.3%).

Of 21 patients who received maintenance therapy, 1 was in the Bor-Dex cohort (1.3%), and 20 were in the CyBorD cohort (27% of the patients who underwent transplantation), $p < 0.001$. Lenalidomide was given to 20 of the 21 patients, including the 1 patient in the Bor-Dex cohort. Bortezomib as maintenance was given to 1 patient in the CyBorD cohort (1.3%).

DISCUSSION AND SUMMARY

This retrospective cohort study based on a real-world clinical experience at a single tertiary care centre enrolled 155 consecutive patients with newly diagnosed MM who received Bor-Dex or CyBorD as first-line therapy before aHSCT. CyBorD replaced Bor-Dex as our standard practice when the relevant phase II studies were published and CyBorD became the standard of care for Canadian transplant-eligible patients with newly diagnosed MM. Response, toxicity, and HSPC collection were influenced by the change in therapy, although first PFS was not statistically prolonged. Bortezomib has recurrently been reported to be a safe and effective anti-myeloma drug[11,12], and with the start of CyBorD as the preferred induction therapy, we saw deeper responses (≥VGPR) in our patients.

As Reece *et al.*[7] showed, side effects associated with bortezomib are usually reversible and are markedly reduced if bortezomib is administered SC in weekly doses. The difference in the bortezomib route and frequency might explain why, compared with the CyBorD cohort, the Bor-Dex cohort in our study tended to require more dose adjustments during induction therapy. On the other hand, a higher number of CD34+ cells per kilogram were collected from patients in the Bor-Dex cohort, with fewer hospital admissions after HSPC mobilization, and a lesser requirement for plerixafor aid in achieving successful HSPC mobilization. Although the difference in plerixafor use might reflect Bor-Dex being given in an era when plerixafor was limited or unavailable, our database notably did not contain a single patient in the Bor-Dex cohort who did not proceed to aHSCT because of HSPC collection failure. Most patients in this study underwent stem-cell mobilization with cyclophosphamide–GCSF, which might have contributed to the higher collection yields in the Bor-Dex cohort and the increased hospitalizations in the CyBorD cohort, because the CyBorD cohort had more exposure to the alkylator. In addition, based on the standard protocols, a slightly higher cumulative dose of bortezomib was given in the CyBorD cohort, which could also have contributed to lower cell yields. Finally, patients in the CyBorD cohort

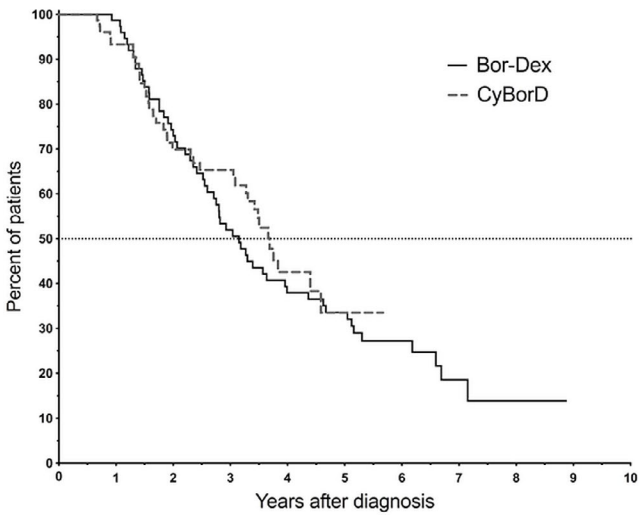

FIGURE 2 Progression-free survival (PFS) from diagnosis to date of first therapy after autologous stem-cell transplantation. Median PFS was 3.7 years after cyclophosphamide–bortezomib–dexamethasone (CyBorD) and 3.2 years after bortezomib–dexamethasone (Bor-Dex), p = 0.56.

were older, which might have played a role in the increased mobilization toxicity and failure rates seen in that cohort. In the more modern CyBorD era, with ready access to plerixafor, many centres have questioned the use of cyclophosphamide as part of mobilization[13] and moved away from it. Patients treated during the CyBorD era had more use of maintenance therapy, which could have contributed to a prolonged PFS—and, ultimately, OS. Unfortunately, maintenance lenalidomide became the standard of care only toward the end of the Bor-Dex era, and we are unable to assess its specific effect on the outcomes or differences in our two cohorts.

Because this is a retrospective cohort study, it has limitations. Standard clinical practice evolved over the study period, resulting in increased use of plerixafor for stem-cell mobilization and use of lenalidomide as maintenance after aHSCT. Those therapies were offered more routinely to patients receiving CyBorD than to those receiving Bor-Dex. A prospective study would be of benefit to overcome the limitations of the present study and other retrospective cohort studies, but such work is unlikely to be undertaken in the modern MM era. We therefore believe that our study still complements current clinical practice.

To our knowledge, ours is the first study to compare the course of treatment involving induction, HSPC collection, and transplantation in transplant-eligible patients with newly diagnosed myeloma receiving Bor-Dex and CyBorD as first-line therapy. Overall, clinical efficacy was similar for the two therapies, but with superior HSPC collection in patients receiving Bor-Dex. Thus, patients receiving CyBorD experienced a deeper response at the cost of fewer HSPCs collected, with no significant additional benefit in long-term disease control after aHSCT. Koproff *et al.*[14] studied the differences in outcome between patients with relapsed or refractory myeloma treated with CyBorD or Bor-Dex, and although those authors looked at a different myeloma population, no clear benefit of adding cyclophosphamide to bortezomib–dexamethasone emerged. Further real-world data concerning those two patient cohorts in the setting of routine access to plerixafor and maintenance lenalidomide would be useful in considering whether the addition of cyclophosphamide to bortezomib–dexamethasone before aHSCT improves outcomes for patients with myeloma.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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