Primary Therapy of Waldenström’s Macroglobulinemia (WM) with Weekly Bortezomib, Low-Dose Dexamethasone and Rituximab (BDR): Long Term Results of a Phase II Study of the European Myeloma Network (EMN)

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Key points

- BDR is an active regimen and induces long lasting responses in patients with newly diagnosed WM
- Induction with single agent bortezomib may be effective in preventing complications of hyperviscosity or rituximab-induced IgM flare

ABSTRACT

In this large phase 2 multicenter trial we evaluated the activity of bortezomib, dexamethasone and rituximab (BDR) combination in previously untreated symptomatic patients with WM. In order to prevent “IgM flare”, an initial cycle of bortezomib (1.3 mg/m² IV days 1,4,8 &11; 21-day cycle), was followed by weekly IV bortezomib (1.6 mg/m² days 1,8,15 &22) every 35 days for 4 additional cycles, followed by IV dexamethasone (40 mg) and IV rituximab (375 mg/m²) in cycles 2 and 5 (total 8 infusions of rituximab). Fifty-nine patients were treated; 45.5% and 40% were high and intermediate risk per ISSWM. On intent-to-treat, 85% responded (3% CR, 7% VGPR, 58% PR, 17% MR). Median IgM reduction after single agent bortezomib was 18% (range -78% to +12%). In 11% of patients an increase of IgM ≥25% was observed after rituximab; no patient required plasmapheresis. After a minimum follow up of 32 months, median PFS is 42 months, 3-year duration of response for patients with ≥PR is 70% and 3-year survival is 81%. Peripheral neuropathy occurred in 46% (grade ≥3 in 7%) but only 8% discontinued bortezomib due to neuropathy. BDR regimen is rapidly acting, well tolerated, non-myelotoxic inducing durable responses in previously untreated WM. Single-agent bortezomib induction was effective in the management of patients with hyperviscosity.

(www.clinicaltrials.gov NCT00981708; European Union Drug Regulating Authorities Clinical Trials number 2006-003563-31)

Key words: Bortezomib, neuropathy, IgM flare, Rituximab, ISSWM
INTRODUCTION

Waldenström’s Macroglobulinemia is a rare B-cell low grade lymphoma, which is characterized by infiltration of the bone marrow by lymphoplasmacytic cells which produce monoclonal immunoglobulin M(IgM). Symptomatic disease is a result of tumor infiltration and/or properties and amount of the monoclonal IgM(1-2). Alkylating agents and nucleoside analogues were the backbone of therapy for WM for several decades. Rituximab has been widely used for the treatment of WM, has minimal toxicity, but as a monotherapy is associated with modest response rates(3-6). Treatment with rituximab is also associated with a transient increase of serum IgM (“IgM flare”) in 30%-80% of patients(3, 7-8) which may exacerbate complications associated with the high levels of paraprotein such as hyperviscosity syndrome(7-8).Combinations of rituximab with chemotherapy (such as the DRC regimen) are associated with better response rates than rituximab alone, however, complete responses are infrequent and median time to response is about 4 months(9). Combinations with more intensive chemotherapy(such as R-CHOP) or nucleoside analogues(such as FR or FCR or cladribine-R) may be associated with higher response rates but at the expense of higher toxicity(10-11).

Novel agents offer an opportunity to improve therapy of WM, by targeting pathways of critical importance for the survival of lymphoplasmacytic cells. Bortezomib is a proteasome inhibitor that targets multiple pathways through inhibition of protein homeostasis within cancer cells, especially plasma cells and lymphoplasmacytic cells(12-14). Bortezomib has shown in vitro activity against WM cells(12-13) and significant clinical activity(15-17). In addition, bortezomib monotherapy can induce rapid reduction of IgM levels(15-16). Furthermore, synergistic activity of bortezomib with rituximab and/or steroids, has been demonstrated in vitro(18-19).

Thus, in 2006 we designed a large phase II study in order to evaluate the activity of the combination of bortezomib, dexamethasone and rituximab (BDR) in previously untreated patients with symptomatic Waldenström’s Macroglobulinemia.
STUDY DESIGN AND TREATMENT

This was a prospective, phase 2, multicenter study which enrolled patients from 10 European sites, within the context of the European Myeloma Network, after approval by national and institutional authorities. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients signed an informed consent before any procedure related to the study. Bortezomib was provided by Janssen-Cilag and rituximab was provided by Hoffman-La Roche.

The primary objective of the study was the determination of response rate [combined complete response (CR) + partial response (PR) + minimal response (MR)] in patients with previously untreated WM. Secondary objectives were the determination of time to progression following treatment with BDR and the assessment of the safety and tolerability of BDR.

The study included patients with the diagnosis of WM based on consensus criteria (20), with symptomatic disease requiring therapy (20-21) who had not received prior therapy. Symptomatic disease was defined by the presence of at least one of the following: B-symptoms, hyperviscosity, lymphadenopathy either symptomatic or bulky (>5 cm maximum diameter), symptomatic hepatomegaly or splenomegaly, organ or tissue infiltration, peripheral neuropathy related to WM, AL amyloidosis related to WM, nephropathy related to WM, symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic anemia and/or thrombocytopenia, hemoglobin <10g/dl, platelets <100x10^9.

Eligible patients had platelets >50x10^9/L, ANC >750x10^6/L, KPS >60%, AST and ALT <3 ULN, total bilirubin <2 ULN and creatinine clearance >30ml/min. Exclusion criteria were prior systemic therapy (plasmapheresis was allowed but per protocol no prophylactic plasmapheresis was mandated), neuropathy with or without pain >grade 2, poorly controlled cardiovascular disorders, mental illnesses, cardiac amyloidosis and pregnant or breastfeeding females.
BDR regimen

A total of 5 cycles of therapy were planned. Treatment consisted of intravenous (IV) bortezomib at a dose of 1.3 mg/m² on days 1,4,8 & 11 for the first 21-day cycle. On cycles 2 to 5 bortezomib was administered weekly IV at a dose of 1.6 mg/m² on days 1,8,15 & 22 in four 35-day consecutive cycles. On cycles 2 & 5 IV dexamethasone 40 mg and IV rituximab at a dose of 375 mg/m² were given on days 1,8,15 & 22 (total of eight infusions of rituximab). Premedication with 1000 mg acetaminophen and 50 mg IV diphenhydramine were given prior to rituximab infusion. In all patients prophylactic valacyclovir or acyclovir for herpes zoster was mandated. Bortezomib could be reduced from 1.6 to 1.3 and 0.8 mg/m² for toxicity.

EFFICACY AND SAFETY ASSESSMENTS: Levels of monoclonal IgM were evaluated after each cycle. CT scans of chest, abdomen and pelvis within 3 months of study enrollment were assessed and repeated after completion of BDR if no monoclonal gammopathy was detected and if screening CTs demonstrated evidence of disease or, if progression of disease was suspected. Patients were followed every 3 months for 2 years after the last dose of study treatment, and every 6 months thereafter. When progressive disease was confirmed patients were removed from the study. All patients that received at least one dose of treatment were eligible for evaluation of response and toxicity. Response was assessed on an intention-to-treat basis. The evaluation of response was performed according to the recommendations of the Third International Workshop for Waldenström’s Macroglobulinemia but data to evaluate cases according to the new criteria were also available (Supplemental Table 1). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC version 3.0).

STATISTICAL ANALYSIS

According to Simon's two-stage optimal design, sample size calculation, was based on the assumption that the expected overall response rate would be ≥70% and the minimum acceptable response rate 50%, for a probability of accepting a treatment with a real response rate <20% of 5% and rejecting a treatment with a response rate >40% of 10%. Progression free survival (PFS) was measured from the date of inclusion in the study until the
date of progression or death by any cause. Overall survival was calculated from the date of inclusion in the study until the date of death or date of last contact. Time to next treatment (TNT) was calculated from the date of first BDR dose until the date of initiation of subsequent therapy. Duration of response was defined by the date of first documentation of response until the date of first evidence of relapse/progression or death. Survival curves were plotted with the method of Kaplan-Meier. Cause of death was defined as a result of the disease or treatment complications, or as death unrelated to WM. Unrelated deaths and WM related deaths, progression or reintroduction of next therapy were considered as competing events for OS, PFS or TNT respectively (24-25). Analysis was performed using SPSS v20 and R software.

RESULTS

From March 2007 until June 2010, sixty patients were enrolled in 5 European countries (Greece, Spain, Italy, France and The Netherlands). One patient did not receive any therapy and was not included in the analysis. Patients’ characteristics are listed in table 1. Median age was 70 years (range 40-83) and median level of serum monoclonal protein was 3.86 g/dl (range 0.17-9.9 g/dl). Most patients had advanced disease and adverse prognostic factors such as advanced age (61% were >65 years), anemia (hemoglobin<11.5 g/dl in 82%) and elevated β2-microglobulin(≥3 mg/dl in 64%). Almost half (45%) were rated as high risk, 40% were at intermediate risk and only 15% at low risk according to ISSWM(26). Primary reasons for initiating treatment were cytopenias (44%), hyperviscosity (20%), B-symptoms (19%) and lymphadenopathy (9%). No patient received prophylactic plasmapheresis before initiation of BDR. Per protocol patients with preexisting neuropathy grade ≥2 were not enrolled in the study. However, 7(12%) patients had mild (grade 1) preexisting neuropathy, one(2%) had cryoglobulinemia and 4(7%) AL amyloidosis.

RESPONSE

Thirty-eight (64%) patients completed the planned 5 courses; 3(5%) received 4 cycles, 7(12%) received 3 cycles, 3(5%) received 2 cycles and 8(14%) patients received only the first cycle of single agent bortezomib. The
overall response rate was 85%(95%CI 73-92%): 2 patients achieved CR(3%), 38(65%) PR and 10(17%) MR; a major response (≥PR) was achieved by 68% (95%CI 55-78%). Four(7%) patients had ≥90% reduction of IgM but had positive immunofixation. Thus, according to the recently proposed criteria(23), the VGPR rate was 7%. Three(5%) patients had SD while 6(10%) were rated as PD(Figure 1B & Table 2).Among patients with evaluable lymphadenopathy, 35% had complete resolution and 40% at least partial resolution of their lymphadenopathy. Splenomegaly resolved completely in 55% and partially in 33% of evaluable patients. Overall, 63% of patients with organomegaly (lymphadenopathy, splenomegaly or both) achieved a response. Among patients who responded, CR, VGPR, PR & MR rates were 6%, 9%, 71% and 14% respectively for those who received all 5 cycles while for responding patients who received less than 5 cycles the VGPR, PR & MR rates were 7%, 57% and 36% respectively (no CRs).Median time to first response (≥MR) was 3 months and median time to best response was 5 months; however, 4(8%) of the responders achieved their best response >6 months after completion of therapy(Figure 1C). No patient required plasmapheresis during therapy with BDR, despite the fact that 44% of the patients had IgM levels≥4000 mg/dl. Among patients(N=28) who had a post treatment bone marrow biopsy, median BM infiltration reduced from 62% to 14% (median reduction 57%) and the respective median IgM reduced from 3835 mg/dl to 1680 mg/dl(median reduction 60%); however, the correlation was not very strong (R²:0.124, p=0.1) IgM levels after bortezomib monotherapy and “IgM Flare”: after the first cycle of single agent bortezomib median reduction of IgM was 18% (range -78% to +12%); 34% patients had ≥25% reduction and 8% had ≥50% reduction)(Figure 1A). In 11% of patients ≥25% increase of IgM was observed after the 2nd cycle of therapy (which included rituximab); the median IgM rise in these patients was 60%(range 39%-219%) and the median absolute increase of IgM was 1614 mg/dl(range 580-4610 mg/dl). This rise of IgM was followed by a subsequent drop of IgM levels after cycle 3 which included bortezomib only. No patient required plasmapheresis for symptomatic hyperviscosity or other complications of the transient IgM increase during therapy with BDR. Among the patients who experienced the IgM rise, 5(50%)
had a PR as their best response, 2(20%) had a MR, 1 had stable disease and 2(20%) were rated as PD. A mild, less pronounced, rise of IgM (median IgM rise 31% and median absolute IgM rise 290 mg/dl, range 170–3440 mg/dl) was also observed in 20% of evaluable patients after the second block of rituximab (cycle 5)- no intervention was required.

**TIME TO PROGRESSION, FURTHER THERAPY AND SURVIVAL**

Minimal follow up after the last patient’s entry in the study is 32 months and median follow up for all patients is 42 months. Until the date of data cutoff (February 1st, 2013), 32(54%) patients experienced disease progression or died (27 had disease progression and 5 died without evidence of disease progression). The estimated median PFS is 42 months, the 3-year cumulative rate of progression is 41% and the 3-year unrelated death rate without progression is 9%. For patients who achieved at least PR the 3-year progression rate is 22.5% and unrelated death rate is 8%(Figure 2A&SupplFig1). The respective 3-year PFS for patients with VGPR or better, PR and MR was 67%, 48% and 30%. Accounting for the competing risk of unrelated death the 3-year risk of progression for patients with a VGPR or better, PR and MR was 0%, 41% and 70% respectively (p=0.02).The 3-year progression probability was 12.5%, 45% and 46% for low, intermediate and high risk patients per ISSWM respectively(p=0.517) and the respective risk of unrelated death was 0%, 4.5% and 8%(p=0.648).PFS for responding patients who received less than 5 cycles was shorter than those who completed 5 courses (28 vs 62 months, p=0.003).

Nineteen patients received further treatment on progression and 84% of them achieved ≥MR. Most (89%) received rituximab-based therapy [DRC(N=6), R-CVP(N=1), rituximab alone(N=1), R-CHOP(N=5), FCR(N=2), bendamustine-rituximab(N=1)]; one patient received FC and one alemtuzumab (no information was available about the type of therapy in one patient). The 3-year rate of subsequent therapy was 28% and 3-year unrelated death rate without subsequent treatment was 7%(SupplFigure1).

Fifteen patients have died; seven patients died due to causes unrelated to WM or therapy (5 of cardiovascular diseases, one died of pneumonia and one due to complications after surgery for lung cancer). The 3-year survival
rate is 82% and the 3-year cumulative incidence of WM-related deaths was 12% and of unrelated deaths was 5%.

There was no significant association of any of the baseline features of the disease (cytopenias, β2-microglobulin, IgM levels, BM infiltration, splenomegaly, lymphadenopathy) or of the patients’ characteristics (age, gender, performance status) or ISSWM with the probability of response (≥MR or ≥PR). Per ISSWM the 3-year progression rate was 30%, 46% and 43% for low, intermediate and high risk group respectively (p=0.8). Serum albumin <3.5 gr/dl was associated with an increased risk of death due to WM (3-year risk of death of 22% vs 0% for those with serum albumin ≥3.5 gr/dl, p=0.03). Risk of death for different ISSWM risk groups was not significantly different, perhaps due to small number of events.

**TOXICITY**

Main reasons for discontinuation of BDR were toxicity in 16 (27%) patients and disease progression (or death) in 5 patients. Toxicities during BDR are depicted in Table 3. Hematologic toxicity included mainly neutropenia (grade ≥3 in 15%) and thrombocytopenia (grade ≥3 in 5%). Peripheral neuropathy of any grade was recorded in 46% (grade 2 in 17% and grade ≥3 in 7%); neuropathic pain was recorded in 20% but was grade 3 in only one patient. In 22 (37%) patients the dose of bortezomib was reduced by at least one dose level due to neuropathy but only 5 (8%) patients discontinued bortezomib due to neuropathy. Among patients with preexisting neuropathy, cryoglobulinemia or AL amyloidosis, the rates and severity of neurotoxicity were similar to that of patients without preexisting neuropathy and most of them completed 5 course of BDR. Infections were common and usually mild—only one patient developed neutropenic fever. One patient developed herpes zoster, after he discontinued prophylaxis with valacyclovir; he received full dose valacyclovir and continued therapy with BDR and prophylaxis. One patient died due to non-neutropenic septic shock. Three (5%) patients experienced pulmonary toxicity which was attributed to bortezomib, consisting of dyspnea, decrease of arterial pO2 and diffuse pulmonary infiltrates on chest CT scan. Pulmonary toxicity in the three patients developed in cycle 1, cycle 4 and cycle 5 respectively and was reversible after
administration of corticosteroids. Two of the 3 patients continued treatment as per protocol and completed 5 cycles of BDR.

**DISCUSSION**

This is the largest phase II trial of a bortezomib-based regimen in WM and with the longest follow up. In previously untreated patients, BDR showed excellent activity, with manageable toxicity and reduced incidence and severity of bortezomib-related neurotoxicity. Importantly, the responses were durable, despite the lack of maintenance. Furthermore, this trial established a European collaboration network for the conduction of clinical studies in a rare disease such as WM.

The current study was designed on the basis of clinical and preclinical data which indicated potential additive/synergistic activity for the combination of bortezomib and rituximab\(^\text{18-19}\). Furthermore, the design of BDR regimen was based on the particular characteristics of WM: besides the tumor load in the BM we also considered the effects of the circulating monoclonal IgM. Accordingly, BDR was designed not as a “lymphoma-like” but as a “WM-specific” therapy. In order to exploit the rapid activity of bortezomib, in terms of IgM reduction, an initial cycle of bortezomib was given before initiation of rituximab, in order to reduce IgM levels and subsequently the frequency and severity of rituximab-associated “IgM flare”. Additionally, we adopted a weekly schedule of administration in order to reduce bortezomib-related neurotoxicity.

The major response rate (CR+VGPR+PR) was 68% (85% including ≥MR) which is higher than any of the drugs alone (≥PR in 30%-50%\((3-7, 15-17, 27)\)), which indicates clinical synergism between bortezomib and rituximab. The median time to first response was 3 months, and compares favorably to rituximab alone [median time to response ≥6 months\((3-4, 6-7)\)]. The median time to best response was 5 months, but some patients achieved their best response several months after completion of BDR despite the fact that there was no maintenance. The response rates in our study are similar to those reported by Ghobrial et al, in a smaller study of bortezomib-rituximab which also did not include maintenance (≥MR in 88%, 8% CR+nCR and 58% PR)\((28)\). In the BDR study by Treon et al\((29)\), responses were higher (≥PR...
83%, CR 13%, nCR 9%, VGPR 13%) perhaps due to the use of maintenance with additional BDR cycles.

The duration of response after BDR is also favorable. In contrast to previous studies (28-29) our study has sufficient follow up to assess PFS, with a long median of 42 months, although there was no maintenance. Notably, 85% of our patients were rated intermediate or high risk per ISSWM. Of note, the 3-year OS is 82% and the 3-year cumulative incidence of WM related deaths is 12% and of unrelated deaths is 5%. The quality of response to primary therapy may be associated with survival in lymphoproliferative disorders. In patients with WM the depth of the response may be associated with longer PFS (30), which is what we also observed in our study, however, several years of follow-up are needed in order to evaluate the effect of the therapy and the quality of response on survival. Future clinical studies should aim at the development of regimens with higher CR rates and reasonable toxicity.

Induction with single agent bortezomib was an effective strategy to manage complications associated with high IgM levels and reduced the need for plasmapheresis and the frequency and severity of rituximab-associated “IgM flare”: only 17% of patients had an IgM rise after rituximab and there was no need for plasmapheresis although 44% of patients had IgM ≥ 4000 mg/dl before initiation of therapy. In comparison, “IgM flare” was observed in 54% of patients treated with single agent rituximab (3, 7), in 32% of patients after DRC (9) and in 31% of patients treated with rituximab-bortezomib (28). In the BDR study by Treon et al, prophylactic plasmapheresis was performed in 26% of patients but 9% had an “IgM flare” requiring plasmapheresis (29).

Toxicity is a major concern for patients with WM, especially since most of them are elderly. BDR had limited myelotoxicity, thus, it may be an attractive option for patients who present with cytopenias or for patients who are candidates for ASCT since none of the drugs is stem cell toxic. The weekly administration of bortezomib was well tolerated, with low rates of clinically significant neuropathy and, importantly, only 8% of patients discontinued bortezomib due to neuropathy, comparing favorably to previously published studies which used a twice-per-week schedule (discontinuation rates of 25%-61% (16-17, 29)), and in accordance with data
from weekly administration of bortezomib with rituximab(28). However, neurotoxicity must be dealt with caution and should be accounted for when physicians decide the most appropriate therapy for patients with WM, because in a disease with a prolonged survival such as WM, neuropathy may seriously affect quality of life. Fortunately, neuropathy was completely reversible in most of our patients. Furthermore, with the current use of subcutaneous bortezomib the problem of peripheral neuropathy it is likely to become less important(31). In addition, the development of novel generation of proteasome inhibitors that seem to be less or not neurotoxic favours the continuous study of the therapeutic impact of proteasome inhibitors in WM.

Pulmonary toxicity is an uncommon complication of bortezomib(32-36). In our study occurred in 5% of patients, but improved rapidly with steroids and standard supportive measures, and actually 2 of 3 patients continued and completed BDR. Physicians who treat patients with bortezomib must be aware of this uncommon complication and evaluate accordingly those patients who present with pulmonary symptoms and initiate steroids if indicated.

Our results justify BDR as an alkylator-free, primary treatment option for patients with WM. The updated results from the phase II study of primary therapy with DRC indicated a median PFS of 35 months and 5-year OS of 62%. BDR is associated with similar response rates and a PFS of 42 months but further follow up is needed for the assessment of survival. Both regimens are active, but with different toxicity profiles and both may be considered as primary therapy in different indications. BDR may be preferable for patients with high levels of IgM, symptoms of hyperviscosity or severe cytopenias while DRC may be preferred for patients with lower levels of IgM, less pronounced cytopenias, IgM-related neuropathy or patients who do not wish to return to hospital frequently for bortezomib injections.

In summary, primary therapy with BDR is safe and effective, associated with maintained responses and excellent PFS in previously untreated patients with WM. Induction with single agent bortezomib effectively reduces IgM levels and may reduce rituximab associated “IgM flare” and the need for plasmapheresis, while weekly administration of bortezomib reduces the risk of neurotoxicity.

Author contribution: MAD designed the study, analyzed data and wrote the manuscript, RGS analyzed and collected data and critically reviewed the manuscript, MG collected and analyzed data and critically reviewed the manuscript, PM analyzed and collected data, performed statistical analysis and critically reviewed the manuscript, MCK, EM, ZK, XL, GP, AT, DG, GM analyzed and collected data and critically reviewed the manuscript, EK analyzed and collected data, performed statistical analysis and wrote the manuscript, PS designed the study, analyzed and collected data and critically reviewed the manuscript.
References


Table 1: characteristics of the patients who were treated with BDR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No of patients</td>
<td>59</td>
</tr>
<tr>
<td>Male / Female</td>
<td>64% / 36%</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>61%</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>43%</td>
</tr>
<tr>
<td>Hyperviscosity syndrome</td>
<td>20%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>43%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>29%</td>
</tr>
<tr>
<td>Hemoglobin &lt; 11.5 gr/dl</td>
<td>82%</td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10^9/L</td>
<td>17%</td>
</tr>
<tr>
<td>Serum IgM&gt; 4000 mg/dl</td>
<td>44%</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 gr/dl</td>
<td>48%</td>
</tr>
<tr>
<td>B2-microglobulin &gt; 3 mg/dl</td>
<td>64%</td>
</tr>
<tr>
<td>Bone marrow lymphocytes (Median / range)</td>
<td>60% (5%-100%)</td>
</tr>
<tr>
<td>Bone marrow lymphocytes ≥ 50%</td>
<td>51%</td>
</tr>
<tr>
<td>ISSWM low / Intermediate / High</td>
<td>15% / 40% / 45%</td>
</tr>
</tbody>
</table>

Table 2: overall response to BDR

<table>
<thead>
<tr>
<th>Response</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>34 (58%)</td>
</tr>
<tr>
<td>MR</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (10%)</td>
</tr>
</tbody>
</table>
Table 3: Toxicity associated with BDR

<table>
<thead>
<tr>
<th></th>
<th>Any Grade (N)</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>10 (17%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (17%)</td>
<td>(5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>27 (46%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>(Sensory)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>(20%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fever NOS</td>
<td>9 (15%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Respiratory Symptoms NOS</td>
<td>9 (15%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Infections NOS</td>
<td>13 (22%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (24%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (19%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (46%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>6 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>8 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal (Increased creatinine)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cardiovascular NOS</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

NOS: Not Otherwise Specified
**Figure 1:** Reduction of IgM levels (A) after each cycle of BDR and at final assessment 3 months post completion of BDR (B) Maximum decrease of the IgM in individual patients (C) time to first (___) and time to best response (___)

**Figure 2:** (A) PFS, (B) Overall survival and (C) cumulative incidence of related and unrelated deaths
Fig 2C

- Related Deaths
- Unrelated Deaths

Probability

Months

0.0 0.2 0.4 0.6 0.8 1.0

0 10 20 30 40 50 60
Primary therapy of Waldenström's macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone and rituximab (BDR): long term results of a phase II study of the European Myeloma Network (EMN)

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