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Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma

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Abstract

The objective of this case-matched study was to compare the efficacy and the toxicity of the addition of clarithromycin (Biaxin) to lenalidomide/low-dose dexamethasone (BiRd) vs lenalidomide/low-dose dexamethasone (Rd) for newly diagnosed myeloma. Data from 72 patients treated at the New York Presbyterian Hospital-Cornell Medical Center were retrospectively compared to an equal number of matched pair mates selected among patients seen at the Mayo Clinic who received Rd. Case matching was blinded and was performed according to age, gender, and transplant status. On intention-to-treat analysis, complete response (45.8% vs 13.9%, $p<0.001$) and very-good-partial-response or better (73.6% vs 33.3%, $p<0.001$) were significantly higher with BiRd. Time-to-progression (median 48.3 vs 27.5 months, $p=0.071$), and progression-free survival (median 48.3 vs 27.5 months, $p=0.044$) were higher with BiRd. There was a trend toward better OS with BiRd (3-year OS: 89.7% vs 73.0%, $p=0.170$). Main grade 3–4 toxicities of BiRd were hematological, in particular thrombocytopenia (23.6% vs 8.3%, $p=0.012$). Infections (16.7% vs 9.7%, $p=0.218$) and dermatological toxicity (12.5% vs 4.2%, $p=0.129$) were higher with Rd.

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Results of this case-control analysis suggest that there is a significant additive value when clarithromycin is added to Rd. Randomized phase III trials are needed to confirm these results.

Keywords

myeloma; newly diagnosed; therapy; lenalidomide

INTRODUCTION

Multiple myeloma (MM) accounts for over 11,000 deaths each year in the United States (1,2). For over 40 years, melphalan and prednisone (MP) remained the standard of care for elderly patients. For more than a decade vincristine, doxorubicin, dexamethasone (VAD) was used as pre-transplant induction therapy for patients eligible for stem cell transplantation (SCT) (2–4). Lenalidomide (CC-5013) is an oral immunomodulatory structural derivative of thalidomide, that is more potent in preclinical assay than the parent drug (5–6). It has a different toxicity profile, with fewer non-hematologic side-effects compared to thalidomide and a more predictable and manageable toxicity (7–8). In newly diagnosed patients, the combination of lenalidomide plus high-dose dexamethasone (RD) was compared with high-dose dexamethasone in a double-blinded placebo-controlled trial and was superior to high-dose dexamethasone in terms of both response rates (complete response [CR] rate: 22.1% vs 3.8%) and 1-year progression-free survival (PFS) (77% vs 55%, $p = 0.002$), but no differences in overall survival (OS) were reported (9). Another recent phase III study compared the combination of lenalidomide plus low-dose dexamethasone (Rd) with the RD regimen: 2-year OS (87% vs 75%, $p < 0.001$) was significantly better with Rd and major grade 3 or higher toxic-effects, including thrombosis (26% vs 12%) and infections (16% vs 9%), were significantly higher in the RD group. These differences were confirmed in both younger and elderly patients (10).

Clarithromycin is an antibiotic that has shown efficacy in association with steroids and both thalidomide(11) and lenalidomide (12). It optimizes the pharmacologic effects of glucocorticoids by increasing the area under the curve and the maximum concentration levels of some steroids (13); it has an immunomodulatory effect (14) and may have direct antineoplastic properties (15).

Based on initial report of moderate activity of thalidomide in heavily pretreated MM, a combination of clarithromycin, thalidomide and low-dose dexamethasone (BLT-D) was studied. This early study yielded results considerably superior to those reported both for thalidomide alone and subsequently for thalidomide and high-dose dexamethasone (without clarithromycin). Among the novel aspects of the BLT-D regimen were the use of weekly dexamethasone and clarithromycin. The putative efficacy was buttressed by a recent report where the same combination of drugs was used: however the dexamethasone was used in high-dose. Results were almost comparable with BLT-D (16).

Because of the putative superiority of lenalidomide over thalidomide, the combination of clarithromycin (Biaxin), lenalidomide and low-dose dexamethasone (BiRd) has been investigated in a phase II study, showing a partial response (PR) rate of 90.3%, including 38.9% CR; 2-year event free survival (EFS) was 97.2% months, and 2-year OS was 90.5%. Major toxic effects were thromboembolic events (12.5%), corticosteroid related morbidity (in particular myopathy in 11.1% of patients) and cytopenia (neutropenia in 19.4% of patients and thrombocytopenia in 22.2% (12).

No comparative study of Rd vs BiRd has been reported so far and none are ongoing or planned. The goal of this retrospective cohort case–matched study was to compare the

efficacy and the toxicity of these two regimens as primary therapy for newly diagnosed MM patients.

MATERIALS AND METHODS

Patients and criteria of matching

A series of 72 patients with newly diagnosed MM who were treated at the New York Presbyterian Hospital–Cornell Medical Center, from December 2004 to November 2006, with BiRd, was analyzed. For comparison of their outcome, an equal number of pair mates were selected among newly diagnosed patients seen at the Mayo Clinic who received Rd, from March 2005 to December 2008. Data were obtained by review of medical records and existing database, after approval from the respective Institutional Review Boards. Case matching was blinded and was performed with respect to age (± 5 years), sex, and transplant (SCT), (patients who received SCT were matched with patients who received SCT; patients who did not receive SCT were matched with patients who did not receive SCT).

Treatment regimen

Patients treated with BiRd were enrolled in a phase II dose-escalating trial conducted at New York Presbyterian Hospital–Cornell Medical Center: lenalidomide was given orally 25 mg/day on days 3 to 21 of cycle 1 and on days 1 to 21 of subsequent cycles; dexamethasone was given orally 40 mg on days 1, 2, 3, 8, 15, and 22 during cycle 1 and weekly on days 1, 8, 15, and 22 of each subsequent cycle; clarithromycin was given orally at a dose of 500 mg twice daily, beginning on day 2 of cycle 1. Each cycle was repeated every 4 weeks.

Patients treated with Rd received lenalidomide at a dose of 25 mg/day, days 1–21 plus low-dose dexamethasone at a dose of 40 mg orally day 1, 8, 15, 22; each cycle was repeated every 4 weeks. Treatment was continued until progression or relapse.

In both treatment groups patients were allowed to discontinue treatment to pursue SCT, but treatment until progression, relapse or unacceptable toxicity was permitted at the physician's discretion.

In both treatment groups patients received antithrombotic prophylaxis with aspirin.

Assessment of efficacy and safety

The response criteria used were standard International Myeloma Working Group (IMWG) Uniform Response Criteria (17). Briefly, a PR was defined as a 50% or higher decrease in the serum monoclonal protein (M-protein) levels from baseline and a greater than 90% reduction in 24-hour urine M-protein excretion (or < 200 mg/24h) (if M-protein was unmeasurable, a 50% or higher decrease in the difference between involved and uninvolved free light chain (FLC) or a 50% or higher reduction in bone marrow plasma cells); for patients with soft tissue plasmacytomas, a 50% size reduction was required. A very good PR (VGPR) required a 90% or greater reduction in serum M-protein and urinary M-protein less than 100 mg/24h or M-protein detectable by immunofixation but not on electrophoresis. A CR was defined as negative serum and urine immunofixation, disappearance of any soft tissue plasmacytoma and less than 5% plasma cells on bone marrow examination. Disease that did not satisfy the criteria for PR, VGPR, CR or progressive disease (PD) was classified as stable disease (SD). Disease progression required any of the following: 25% or greater increase in serum M-protein (absolute ≥ 0.5 g/dL) or urine M-protein (absolute ≥ 200 mg/dL) or, in case of unmeasurable M-protein, in the difference between involved and uninvolved FLC (absolute > 10 mg/dL) or 25% increase in bone marrow plasma cell percentage; development of new bone lesions, plasmacytomas; or disease-related

hypercalcemia. All responses needed to be confirmed at least in two consecutive assessments. Time to progression (TTP) was calculated from start of therapy until progression, relapse or last known remission (death for causes other than progression were censored); PFS was calculated from start of therapy until the date of progression, relapse, death from any cause, or known remission; time to next treatment (TTNT) was calculated from the start of therapy until the date the patient received a new alternative treatment; OS was calculated from start of therapy until the date of death or the date the patient was last known to be alive. All adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria (version 3.0) (18).

Statistical Analysis

The endpoint of this study was to compare the efficacy (response rate, PFS, TTP, TTNT and OS) and the toxicity profile (rate of grade 3–4 AEs) of these two regimens. Outcome was analyzed on an intention-to-treat basis. The Chi-square test or two-sided Fisher exact test were used to compare differences in nominal variables and the rank sum test was used for continuous variables. Time-to-event analysis was performed using the Kaplan-Meier method (19). All comparisons were determined by the log-rank test and by the Cox proportional hazards model to estimate crude hazard ratios (HRs) and 95% confidence intervals (95% CIs). Analyses were performed using SAS software, version 9.1. Times of observation were censored on May 2009 for Rd patients and on March, 2009 for BiRd patients.

RESULTS

Patient characteristics

Patient characteristics are listed on Table 1. Baseline characteristics were similar; the two groups were comparable with respect to the major variables known to affect outcome. A similar proportion of patients in the two groups presented with International Staging System (ISS) Stage I or II at diagnosis (80.3% vs 74.2%, $p = 0.402$).

In both treatment groups, 44.4% of patients received SCT at some point during the course of the disease; 38.8% of patients in BiRd group and 34.7% of patients in Rd group received a SCT upfront, defined as part of first line treatment.

Response to Therapy

Based on standard IMWG criteria, the response rate was significantly higher in BiRd patients compared to Rd (Table 2). In an intention-to-treat analysis, a CR was achieved in the BiRd group in 45.8% versus 13.9% in the Rd group, ($p < 0.001$), and 73.6% vs 33.3%, respectively ($p < 0.001$) achieved at least a VGPR. Median duration of treatment was longer in BiRd patients compared to Rd patients (11.8 vs 6.0 months). Response rates, for BiRd and Rd patients who completed 6 months and 1 year of treatment, were evaluated. CRs were higher in BiRd group, but the difference was not statistically significant; VGPR rate was significantly higher for BiRd patients both after 6 months of therapy (56.7% vs 35.0%, $p = 0.033$) and after 1 year (72.2% vs 44.4%, $p = 0.046$).

Survival

The median duration of follow-up for survivors from diagnosis was 37.3 months in the BiRd group and 15.7 months in the Rd group. A similar proportion of patients was still receiving treatment at the time of analysis in the two groups (20.8% vs 23.6%, respectively in the BiRd group and Rd group, $p = 0.689$). In the following analysis, patients who received SCT and patients who switched to another chemotherapy regimen before progression were censored at the date of transplant or chemotherapy change.

TTP was longer in the BiRd group (median 48.3 months) than in patients receiving Rd (median 27.5 months) (HR 0.51; 95% CI 0.25–1.06; $p = 0.071$), (Figure 1A). Similarly, PFS was longer in BiRd patients (median values: 48.3 months vs 27.5 months, HR 0.50; 95% CI 0.25–0.98; $p = 0.044$) (Figure 1B). The previous analyses were repeated without censoring patients who received SCT or switched to another chemotherapy regimen: both TTP (Figure 1C) and PFS (Figure 1D) were significantly longer in BiRd group. The median TTNT was not reached in the BiRd group compared to 29.9 months in the Rd patients (HR 0.36 95% CI 0.20–0.66; $p < 0.001$), (Fig 2A).

Overall survival was not significantly different between the two groups (3-year OS: 89.7% vs 73.0% in the BiRd and Rd groups, respectively, HR 0.48; 95% CI 0.17–1.37; $p = 0.170$), (Fig 2B). Early deaths (during the first 4 months of therapy) were reported in 2/72 (2.8%) in BiRd group and none in the Rd group, respectively ($p = 0.497$).

Subgroup analysis

According to ISS stage, in patients presenting with ISS stage I/II, TTP (median: 48.3 vs 23.2 months, HR 0.38; 95% CI 0.15–0.94; $p = 0.036$), PFS (median: 48.3 vs 23.2 months, HR 0.41; 95% CI 0.17–0.99; $p = 0.047$) and TTNT (median: 48.3 vs 23.2 months, HR 0.34; 95% CI 0.16–0.71; $p = 0.004$) were all significantly longer in BiRd patients, compared to Rd patients; no significant differences in TTP, PFS and TTNT were found among patients with stage III ISS treated with BiRd or Rd. OS was not different between the 2 groups regardless of ISS stage.

By subgroup analyses, the OS was higher in BiRd patients, both considering patients who received SCT (2 year OS: 93.5% vs 80.9%, HR 0.35; 95% CI 0.06–2.17; $p = 0.262$) and patients who did not (2 year OS: 86.6% vs 64.7%, HR 0.56; 95% CI 0.16–2.02; $p = 0.375$) (Fig 3A and 3B).

Toxicity and deaths

Major grade 3–4 toxicities with BiRd and Rd are listed in Table 3. Fifty-five (76.4%) patients receiving BiRd and 42 (58.3%) patients receiving Rd experienced at least one grade 3 or higher toxicity ($p = 0.021$). The frequency of neutropenia was similar between the 2 groups while thrombocytopenia was significantly more frequent with BiRd (23.6% vs 8.3%, $p = 0.012$). One of the most common extra-hematological toxicities reported with BiRd was steroid related myopathy, which was significantly higher than with Rd (9.7% vs 0%, $p = 0.013$).

The most common toxicities in patients treated with Rd were infections (16.7% vs 9.7%, $p = 0.218$) and dermatological toxicities (12.5% vs 4.2%, $p = 0.129$). The rate of thromboembolic events (VTE) was similar in the two groups (12.5% vs 9.7%, respectively in Rd and BiRd, $p = 0.596$). Seven (9.7%) patients treated with BiRd discontinued treatment for AEs compared to 9 (12.5%) patients receiving Rd ($p = 0.596$). There were 2 toxic deaths in BiRd (pulmonary embolism [1] and myocardial infarction [1]) and none in Rd.

DISCUSSION

In newly diagnosed MM patients, two randomized studies have demonstrated the efficacy of the combination of lenalidomide plus dexamethasone. Preliminary results showed that RD resulted in a higher CR rate and 1-year PFS than did high-dose dexamethasone (9). The Rd combination showed further benefit in terms of 2-year OS compared to RD, with a lower rate of grade 3 or higher toxic-effects, related to the use of lower steroid doses. Therefore the trial was halted and RD patients were crossed over to RD: as a consequence OS survival curves merged at 3 years. The regimen was well tolerated in younger and older patients (10).

The addition of clarithromycin to Rd has produced a CR rate of 38.9%, and 2-year EFS of 97.2% (12). Clarithromycin probably optimizes the pharmacologic effects of glucocorticoids, and this can in part explain why one of the major corticosteroid-related toxicities reported was myopathy. It has also an immunomodulatory effect and may have direct antineoplastic properties. It is unclear if clarithromycin can in some way affect the pharmacologic effects of lenalidomide, but unlikely since lenalidomide is not target for microsomal P450 or cytochrome 3A4. However direct pharmacokinetics studies to confirm this are warranted.

No formal comparison has been done so far between Rd and BiRd. In an attempt to address this issue, to determine the additive value of clarithromycin compared to a regimen of lenalidomide plus low-dose corticosteroid, we performed a case-match analysis that adjusted for age, gender and transplantation status. The two groups were comparable for baseline characteristics and for the main prognostic factors known to affect outcome. With the exception of clarithromycin, the treatment regimens were virtually identical; the dose of dexamethasone was the same in both Rd and BiRd with the exception of two extra doses of dexamethasone in the first cycle with BiRd. It is doubtful that two extra doses of dexamethasone would explain the magnitude of the differences observed.

On intention-to-treat analysis, CR and VGPR rates were significantly higher with BiRd. Since duration of treatment was significantly longer for BiRd patients, we evaluated response rates after 6 months and 1 year of therapy, and the results were unchanged. A longer duration of therapy seems to be related in both groups to an increase in response rates, however more pronounced in BiRd than in Rd, resulting in a significantly higher response with BiRd regardless of the duration of therapy. TTP, PFS and TTNT were also significantly better in patients treated with BiRd. This translated in an increase in OS, even if the difference lacks significance so far. We adjusted for the effect of transplantation, by comparing the two regimens in patients who received transplantation as well as in the subset of patients who did not, and the findings were sustained. All these findings suggest benefit in terms of both response rate and survival, related to the addition of clarithromycin to Rd. If this benefit is related to the optimization of the steroid effects or to a direct antineoplastic activity it is still unknown.

The AEs reported were consistent with the established toxicity profile for both regimens. The rate of grade 3–4 AEs was higher in BiRd group, with an increase in both steroid- and lenalidomide-related toxicity. The rate of steroid-related toxicity (myopathy and neurological toxicity in particular) was higher with BiRd than with Rd, which supports the hypothesis that the benefit of clarithromycin is due to an increase in steroid effect. Hematological toxicity was also higher with BiRd but this did not translate into an increase in infections, in part likely related to the antibiotic effect of clarithromycin. Except for hematological toxicity, other lenalidomide-related toxicity (VTE and dermatological toxicity) were not more frequent in the BiRd group. Despite a higher rate of grade 3–4 AEs, treatment discontinuation due to AEs was similar in both groups. Duration of therapy was definitely longer for BiRd patients. It is however hard to say if the longer duration of therapy is due to a better tolerability of this regimen (despite a higher rate of AEs) or is simply a consequence of a difference in clinical practice.

There are some limitations to our analysis. Since patients treated with Rd were a mix of patients enrolled in clinical trials and patients who received therapy outside of a clinical study, the rates of toxicity in Rd may be underestimated. Another limitation is that, since patients were treated in two different institutions, a difference in clinical approach, such as duration of therapy, could have affected the results. Despite these limitations, this is the first study to compare the efficacy and safety of these two regimens.

In summary, results of this case-control analysis suggest the superiority of BiRd compared to Rd in terms of response rates and survival. It is worth noting that clarithromycin is an excellent antibiotic, and that antibiotics are routinely recommended for patients receiving steroid-based induction in almost all clinical trials and in practice. BiRd treatment, although more active was associated with increased toxicity, in particular hematological toxicity (without an increase in infections, at least in part related to the effect of clarithromycin) and steroid-related toxicity; treatment was overall well tolerated. Randomized prospective phase III studies are necessary to confirm these results. Comparisons of BiRd with other active regimens such as bortezomib/dexamethasone and bortezomib/thalidomide/dexamethasone are also needed to determine the optimum initial therapy for multiple myeloma.

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Figure 1A

Figure 1B

Figure 1C

Figure 1D

Figure 1. Time-to-progression (TTP) and progression-free survival (PFS) in the intention-to-treat-population of patients treated with clarithromycin-lenalidomide-low-dose dexamethasone (BiRd) and lenalidomide-low-dose dexamethasone (Rd)

Panel A: TTP; panel B: PFS; censoring patients at transplant date. Panel C: TTP; panel D: PFS, not censoring patients at transplant date. Median TTP/PFS are provided in the figure (m: months).

Figure 2A

Figure 2B

Figure 2. Time to next treatment (TTNT) and overall survival (OS) in the intention-to-treat-population of patients treated with clarithromycin plus lenalidomide-low-dose dexamethasone (BiRd) and lenalidomide plus low-dose dexamethasone (Rd)

Panel A shows TTNT; panel B shows OS. Median TTNT and OS are provided in the figure (m: months)

Figure 3A

Figure 3B

Figure 3. Subgroup analysis of overall survival (OS) in the intention-to-treat-population of patients treated with clarithromycin plus lenalidomide-low-dose dexamethasone (BiRd) and lenalidomide plus low-dose dexamethasone (Rd)

Panel A shows OS in patients who received transplant; panel B shows OS in patients who did not receive transplant. Median OS is provided in the figure (m: months)

Table 1

Patient Characteristics

	BiRd (n=72)	Rd (n=72)	P-value
	N (%)	N (%)	
Age – median, (range) years	62.6 (35.5–81.5)	62.5 (36.0–83.0)	0.906
< 65	40 (55.6)	39 (54.2)	0.867
Sex – no. of patients (%)			
Male	41 (56.9)	41 (56.9)	-
LDH- median, (range)	169 (78–589)	153 (88–395)	0.09
CRP- median, (range)	0.38 (0.02–14.2)	0.32 (0.04–13.6)	0.416
International Staging System			
I/II*	57 (80.3)	46 (74.2)	0.402
III*	14 (19.7)	16 (25.8)	0.402
Missing	1 (1.4)	10 (13.9)	-
Type of M protein			
IgG	44 (61.1)	47 (65.3)	0.604
IgA	16 (22.2)	12 (16.7)	0.400
Light-chain only/BJ#	12 (16.7)#	10 (13.9)	0.643
Missing	0 (0)	2 (2.8)	-
No M-protein	0 (0)	1 (1.4)	1.000
Transplant	32 (44.4)	32 (44.4)	-

BiRd: clarithromycin/lenalidomide/low-dose dexamethasone; Rd: lenalidomide/low-dose dexamethasone;

* percentage calculated on number of patients whose data were available.

Table 2

Responses to Treatment.

	Best responses			Response rate at 6 months			Response rate at 1 year		
	BiRd N (%) N	Rd N (%)	P-value	BiRd N (%) N	Rd N (%)	P-value	BiRd N (%) N	Rd N (%)	P-value
	N= 72	N= 72		N= 60	N= 40		N= 36	N= 18	
CR or VGPR	53 (73.6)	24 (33.3)	<0.001	34 (56.7)	14 (35.0)	0.033	26 (72.2)	8 (44.4)	0.046
CR	33 (45.8)	10 (13.9)	<0.001	11 (18.3)	5 (12.5)	0.580	13 (36.1)	5 (27.8)	0.760
VGPR	20 (27.8)	14 (19.4)	0.239	23 (38.3)	9 (22.5)	0.096	13 (36.1)	3 (16.6)	0.209
PR	12 (16.7)	33 (45.8)	<0.001	22 (36.7)	16 (40.0)	0.736	8 (22.2)	2 (11.1)	0.466
SD	4 (5.6)	9 (12.5)	0.244	0 (0)	0 (0)	-	0	0	-
PD	0 (0)	2 (2.8)	0.497	0 (0)	1 (2.5)	0.400	0 (0)	2 (11.1)	0.107
NA	3 (4.2)	4 (5.6)	-	4 (6.7)	9 (22.5)	-	2 (5.6)	6 (33.3)	-

BiRd: clarithromycin/lenalidomide/low-dose dexamethasone; Rd: lenalidomide/low-dose dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available. Percentage may not total 100 because of rounding.

Table 3

Grade 3–4 Adverse Events

	BiRd N= 72	Rd N= 72	P value
	N (%)	N (%)	
Grade 3/4 Adverse Events	55 (76.4)	42 (58.3)	0.021
Hematological Adverse Events			
Anemia	13 (18.1)	4 (5.6)	0.036
Thrombocytopenia	17 (23.6)	6 (8.3)	0.012
Neutropenia	14 (19.4)	12 (16.7)	0.665
Leukopenia (no associated neutropenia)	5 (6.9)	0 (0)	0.058
Extra-Hematological Adverse Events			
Gastro-intestinal toxicity	11 (15.3)	5 (6.9)	0.184
GI Bleeding	1 (1.4)	1 (1.4)	1.000
Perforated Colon	3 (4.2)	0 (0)	0.245
Abdominal Abscess	1 (1.4)	0 (0)	1.000
Pancreatitis	0 (0)	1 (1.4)	1.000
Venous thromboembolism	7 (9.7)	9 (12.5)	0.596
Deep vein thrombosis	5 (6.9)	8 (11.1)	0.562
Pulmonary embolism	2 (2.8)	1 (1.4)	1.000
Dermatological	3 (4.2)	9 (12.5)	0.129
Infections			
Pneumonia	3 (4.2)	5 (6.9)	0.719
Sepsis	2 (2.8)	2 (2.8)	1.000
Cardiovascular	4 (5.6)	4 (5.6)	1.000
Edema	2 (2.8)	0 (0)	0.497
Fatigue	2 (2.8)	3 (4.2)	1.000
Myopathy	7 (9.7)	0 (0)	0.013
Tremor	2 (2.8)	0 (0)	0.497
Mood alteration	3 (4.2)	0 (0)	0.245
Steroid induced psychosis	1 (1.4)	0 (0)	1.000
Anxiety/depression	2 (2.8)	1 (1.4)	1.000
Transaminase increase	0 (0)	2 (2.8)	0.497
Electrolytic Disturbances	5 (6.9)	1 (1.4)	0.209
Hyperglycemia	2 (2.8)	1 (1.4)	1.000
Renal Failure/creatinine increase	2 (2.8)	3 (4.2)	1.000

BiRd: clarithromycin/lenalidomide/low-dose dexamethasone; Rd: lenalidomide/low-dose dexamethasone