Original Article

Lenalidomide with Dexamethasone to Multiple Myeloma Patients Relapsing from Bortezomib-Based Induction Therapies: A Prospective, Observational Study

Tran-Der Tan[1#], Ying-Chung Hong[2#], Sin-Syue Li[3,4], Jui-Ting Yu[5], Yung-Chuan Sung[6,7], Po-Nan Wang[8*], Chieh-Lin Jerry Teng[9,10,11*]

[1]Hematology and Medical Oncology, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan, [2]Division of Hematology and Oncology, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [3]Division of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [4]College of Medicine, National Cheng Kung University, Tainan, Taiwan, [5]Division of Hematology/Medical Oncology, Department of Medicine, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan, [6]Division of Hematology/Oncology, Department of Medicine, Cathay General Hospital, Taipei, Taiwan, [7]School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan, [8]Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [9]Division of Hematology/Medical Oncology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, [10]Department of Life Science, Tunghai University, Taichung City, Taiwan, [11]School of Medicine, Chung Shan Medical University, Taichung City, Taiwan

Abstract

Lenalidomide with dexamethasone (Len/Dex) is considered to be an effective and well-tolerated regimen to treat multiple myeloma (MM) patients relapsing after bortezomib induction therapy. With the increase in novel agents targeting refractory and relapsed MM, the identification of clinical or laboratory variables that can predict the appropriate candidates of Len/Dex is essential. To address this question, we prospectively assessed 38 adult MM patients who received bortezomib-based induction therapy and were administered Len/Dex for their first relapse. These 38 patients were stratified into the symptomatic relapse group ($n = 10$) and biological relapse group ($n = 28$) according to the disease status when Len/Dex was initiated. The overall response rate in the symptomatic group and biological relapse group was 70.0% (7/10) and 60.7% (17/28), respectively ($P = 0.964$). These two groups harbored a comparable median Len/Dex treatment duration (139 vs. 225 days; $P = 0.876$) and progression-free survival 2 (PFS2) (501 vs. 1289 days; $P = 0.410$). Multivariate analyses failed to show that treating biological relapse (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 0.43–3.88; $P = 0.648$), PFS with bortezomib-based induction therapies ≥18 months (HR: 1.79; 95% CI: 0.64–5.01; $P = 0.266$), autologous hematopoietic stem cell transplantation (HR: 2.18; 95% CI: 0.56–8.55; $P = 0.262$), and high-risk cytogenetics (HR: 0.85; 95% CI: 0.18–3.93; $P = 0.835$) were attributed to depth of Len/Dex treatment. In conclusion, whether MM patients treated by Len/Dex for biological relapse would have a better outcome than those prescribed for symptomatic relapse remains inconclusive. Treating significant biological relapse and symptomatic relapse remains the current consensus.

Keywords: Cytogenetics, lenalidomide, multiple myeloma, relapse, treatment response

Introduction

Multiple myeloma (MM) is a hematological malignancy originating from abnormal plasma cell proliferation. Anemia, bone pain, hypercalcemia, and renal function impairment are the classical manifestations of MM.[1] In the past decades, the treatment outcome of MM has significantly improved; bortezomib becoming one of the front-line therapies is one reason for such improvements. Compared to melphalan and prednisolone, bortezomib plus velcade, melphalan, and

Received: 13-Aug-2020 **Revised:** 01-Sep-2020 **Accepted:** 09-Sep-2020
Published: 27-Oct-2020

Supplementary material available online

Access this article online

Quick Response Code:

Website: www.cjphysiology.org

DOI: 10.4103/CJP.CJP_68_20

***Address for correspondence:** Dr. Po-Nan Wang, No. 5, Fuxing Street, Guishan, Taoyuan City 33305, Taiwan.
E-mail: dwang1415@gmail.com
Dr. Chieh-Lin Jerry Teng, No. 1650, Taiwan Boulevard Section 4, Taichung City 40705, Taiwan.
E-mail: drteng@vghtc.gov.tw
[#]These authors are equally contributed to this work

How to cite this article: Tan TD, Hong YC, Li SS, Yu JT, Sung YC, Wang PN, *et al*. Lenalidomide with dexamethasone to multiple myeloma patients relapsing from bortezomib-based induction therapies: A prospective, observational study. Chin J Physiol 2020;63:211-7.

prednisone provides transplant-ineligible newly diagnosed MM patients with a more favorable progression-free survival (PFS) as well as superior overall survival (OS).[2] Besides, with a more than 80% response rate, both bortezomib-Velcade, thalidomide-dexamethasone (VTD), and bortezomib Velcade-cyclophosphamide-dexamethasone are effective front-line treatments to transplant-eligible myeloma patients.[3] However, MM remains an incurable disease. The majority of the MM patients having been successfully treated by bortezomib-based induction regimens eventually suffer from disease relapses. Therefore, the identification of an effective and well-tolerated therapy for patients relapsing after bortezomib induction is crucial.

Among the therapeutic agents available to MM patients relapsing from bortezomib-based induction, lenalidomide is of importance. As a derivative of thalidomide, lenalidomide is an immunomodulatory drug, targeting myeloma cells by various mechanisms.[4] The combination of lenalidomide and dexamethasone (Len/Dex) was the first regimen officially introducing to refractory and relapsed MM (RRMM) treatments according to the results of the MM-009[5] and MM-010[6] studies. With an overall response rate of 60.6%, the median PFS and OS in RRMM patients receiving Len/Dex treatment were 13.4 and 38.0 months, respectively.[7] However, the real-world effectiveness of Len/Dex in these particular patients is usually inferior to that from clinical trials. In accordance, a retrospective study by Jo *et al*.[8] demonstrated that the PFS and OS in RRMM patients treated by Len/Dex were only 11.2 and 25.5 months, respectively.

Because most Len/Dex studies have focused on RRMM patients with various lines of previous therapies, the efficacy and safety of second-line Len/Dex to MM patients relapsing from bortezomib-based front-line treatments remains unclear. In addition, combinations of novel agents in the Len/Dex regimen for RRMM have shown superior PFS and OS than Len/Dex alone.[9-12] However, triplet regimens usually result in more medical and financial adverse events than do doublet regimens. The identification of clinical or laboratory variables that are the best candidates for Len/Dex doublet treatment is essential. Besides, the timing of the second-line Len/Dex initiation also needs further investigation.

Therefore, in this prospective, observational study, we evaluated the clinical characteristics and cytogenetics in first relapsed MM patients who previously underwent bortezomib-based induction therapy. We also compared the Len/Dex treatment duration and PFS2 among patients treated with second-line Len/Dex for biological and symptomatic relapses. Variables attributed to Len/Dex treatment response were also studied.

Materials and Methods

Patients

This multicenter prospective observational study was approved by the review board of institutions participating in this research (Koo Foundation Sun Yat-Sen Cancer Center: 20161102A, Kaohsiung Veterans General Hospital: VGHKS17-CT1-04, National Cheng Kung University Hospital: A-ER-106-097, Tungs' Taichung MetroHarbor Hospital: 105071, Cathay General Hospital: CGH-P106008, and Taichung Veterans General Hospital: CE16204A-3) and has conducted in accordance with the Declaration of Helsinki. Under written informed consent, 41 MM patients ≥20 years of age who had been previously treated with bortezomib-based induction therapies and had planned to undergo the Len/Dex treatment regimen for their first relapse from September 2016 to March 2020 were screened and entered in to this study. We excluded three patients who received chemotherapeutic agents other than Len/Dex. Finally, the data of 38 patients were analyzed. Patients were further stratified into the symptomatic relapse group (n = 10) and biological relapse group (n = 28) according to the disease status when the Len/Dex regimen was initiated [Supplemental Table 1].[13] The decision for Len/Dex treatment for symptomatic relapse or biological relapse was made by both the investigators and patients.

Dose adjustment and adverse events

The Len/Dex regimen in the current study contained daily lenalidomide 25 mg and weekly dexamethasone 20 mg on day 1–21 during each 28-day cycle. We used the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.0) to assess the Len/Dex regimen's toxicities. For patients with grade 3–4, adverse events attributed to Len/Dex treatment, the lenalidomide dose was adjusted by a sequential reduction of 25, 15, 10, and 5 mg.[6]

Outcome measures

We used the International Myeloma Working Group consensus criteria to evaluate the Len/Dex treatment response.[14] Patients with complete response, very good partial response (PR), and PR were defined to be responders. Non-responders were patients with stable disease or refractory disease after Len/Dex treatment.

Cytogenetic features in patients relapsing from bortezomib-based regimens were another outcome measure in the current study. We used fluorescence *in situ* hybridization to identify cytogenetics of del(17p), del(13q), t(11; 14), t(4; 14), and t(14; 16). The results were defined positive when more than 10% of plasma cells were enriched by CD138 positive selection had these cytogenetic abnormalities. Patients with del(17p), t(4; 14), and t(14; 16) were considered to be cytogenetically high risk.[15]

We also investigated whether the type of MM relapse would impact the Len/Dex treatment outcome. To answer this question, we compared Len/Dex treatment duration and PFS2 between the symptomatic relapse group and biological relapse group. The PFS2 was defined as the period from the date of bortezomib initiation to the date of Len/Dex cessation due to the progression or the end of the analysis (May 15, 2020).

Table 1: Comparison of clinical characteristics among relapsed myeloma patients treated for symptomatic and biochemical relapses

	All patients (*n*=38)	Symptomatic relapse (*n*=10)	Biochemical relapse (*n*=28)	*P*
Age, median, years (range)	62.5 (45-87)	65.0 (47.0-87.0)	61.5 (45.0-86.0)	0.546[a]
Gender, *n* (%)				
Female	20 (52.6)	4 (40.0)	16 (57.1)	0.468[b]
Male	18 (47.4)	6 (60.0)	12 (42.9)	
ISS, *n* (%)				
I	9 (25.7)	4 (40.0)	5 (20.0)	0.079[b]
II	9 (25.7)	0	9 (36.0)	
III	17 (48.6)	6 (60.0)	11 (44.0)	
DSS, *n* (%)				
I	3 (8.3)	1 (10.0)	2 (7.7)	0.419[b]
II	4 (11.1)	0	4 (15.4)	
III	29 (80.6)	9 (90.0)	20 (76.9)	
Disease subtypes, *n* (%)				
IgG	15 (39.5)	2 (20.0)	13 (46.4)	0.251[b]
IgA	11 (28.9)	3 (30.0)	8 (28.6)	
Light chain disease	12 (31.6)	5 (50.0)	7 (25.0)	
First line treatment, *n* (%)				
VTD	33 (86.8)	9 (90.0)	24 (85.7)	0.645[b]
VCD	1 (2.6)	0	1 (3.6)	
VD	2 (5.3)	1 (10.0)	1 (3.6)	
VMP	2 (5.3)	0	2 (7.1)	
Auto-HSCT, *n* (%)				
Yes	20 (52.6)	2 (20.0)	18 (64.3)	0.027[b]
No	18 (47.4)	8 (80.0)	10 (35.7)	
Best response by first line treatment				
CR	16 (42.1)	4 (40.0)	12 (42.9)	0.093[b]
VGPR	15 (39.5)	2 (20.0)	13 (46.4)	
PR	7 (18.4)	4 (40.0)	3 (10.7)	
Reasons to withdraw first line therapy, *n* (%)				
Complete therapy	35 (92.1)	8 (80.0)	27 (96.4)	0.046
Disease progression	2 (5.3)	2 (20.0)	0	
Refractory disease	0	0	0	
Adverse events	1 (2.6)	0	1 (3.6)	
PFS by first line treatment, median, days (range)	599 (196-2275)	388.5 (196-1554)	709.5 (236-2275)	0.101[a]

[a]Data were compared between symptomatic and biochemical relapse groups by using the Mann–Whitney U-test, [b]Data were compared between symptomatic and biochemical relapse groups by using the Chi-square test. *n*: Number, ISS: International Staging System, DSS: Durie–Salmon staging system, IgG: Immunoglobulin G, IgA: Immunoglobulin A, VTD: Velcade, thalidomide, and dexamethasone, VCD: Velcade, cyclophosphamide, and dexamethasone, VD: Velcade and dexamethasone, VMP: Velcade, melphalan, and prednisolone, Auto-HSCT: Autologous hematopoietic stem cell transplantation, CR: Complete remission, VGPR: Very good partial response, PR: Partial response, PFS: Progression-free survival

Statistical analysis

The Mann–Whitney U-test was used to compare the continuous variables between the symptomatic and biological relapse groups. Chi-squared tests were used to compare the categorical variables. The treatment duration of Len/Dex and PFS2 were analyzed using the log-rank test. Variables attributed to responsive Len/Dex treatment were investigated by the Cox-proportional hazards regression, as quantified by hazard ratios (HRs) and accompanying 95% confidence intervals (CIs). The results were considered statistically significant when $P < 0.05$. We used the SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) to conduct all statistical analyses.

Results

Patient demographics

The median age of the 38 patients in the current study was 62.5 (range: 45–87) years. In the study cohort, 80.6% (29/38) were Durie-Salmon stage (DSS) III at initial diagnosis. Using an international staging system (ISS), 48.6% (17/38) of patients were found to have stage III MM. The majority of the patients underwent VTD induction therapy, accounting for 86.8% (33/38). With respect to autologous hematopoietic stem cell transplantation (auto-HSCT), 52.6% (20/38) of our patients had undergone auto-HSCT as part of their frontline

therapy. The median PFS after the first-line therapy was 599 days (range: 196–2275).

In terms of clinical characteristic comparisons among relapsed MM patients treated for symptomatic and biological relapses, these two groups of patients had a comparable age ($P = 0.546$), gender ($P = 0.468$), stages at diagnosis ($P = 0.079$ for ISS; $P = 0.419$ for DSS), types of induction therapies ($P = 0.645$), best response by the first-line induction therapies ($P = 0.093$), and PFS ($P = 0.101$). Of note, patients who started Len/Dex treatment for biological relapse were significantly more likely to have undergone auto-HSCT as part of the front-line therapy than patients with symptomatic relapse (64.3% vs. 20.0%; $P = 0.027$) [Table 1].

Cytogenetic abnormalities of MM patients relapsing after bortezomib-based induction therapies

Regarding the cytogenetic features of MM patients relapsing after bortezomib-based induction therapies, 10.5% (4/38), 31.6% (12/38), 5.3% (2/38), and 5.3% (2/38) of patients had del(17p), del(13q), t(11; 14), and t(4; 14) abnormalities, respectively. These cytogenetic abnormalities were not significantly different among patients in the symptomatic and biological relapse groups ($P = 0.556$ for del(17p); $P = 1.000$ for del(13q); $P = 1.000$ for t[11; 14]; $P = 1.000$ for t[4; 14]) [Table 2].

Outcome comparisons between MM patients treated with Len/Dex for biological and symptomatic relapses

Table 2 summarized the outcome comparisons between the two groups. Briefly, the overall response rate of the study cohorts treated with Len/Dex for their first relapse after bortezomib-based induction therapies was 63.1% (24/38). The overall response rate in the symptomatic group and biological relapse group was 70.0% (7/10) and 60.7% (17/28), respectively ($P = 0.964$). In the symptomatic relapse group, 87.5% (7/10) of patients stopped Len/Dex treatment because of disease progression compared to 61.9% (13/28) of patients in the biological relapse group.

In terms of Len/Dex treatment duration and PFS2, the median Len/Dex treatment duration for patients in the symptomatic group and biological relapse was 139 and 225 days, respectively ($P = 0.876$) [Figure 1a]. Moreover, these two groups of patients had a comparable median PFS2 (501 vs. 1289 days; $P = 0.410$) [Figure 1b].

Variables attributed to depth of Len/Dex treatment

We also investigated the possible variables attributed to Len/Dex treatment response. The univariate analysis showed the age (HR: 1.01; 95% CI: 0.97–1.06; $P = 0.563$), sex (HR: 0.69; 95% CI: 0.30–1.61; $P = 0.396$), PFS by bortezomib-based induction therapies ≥18 months (HR: 1.67; 95% CI: 0.67–4.18; $P = 0.270$), auto-HSCT (HR: 1.14; 95% CI: 0.49–2.64; $P = 0.767$), and high-risk cytogenetics (HR: 1.53; 95% CI: 0.44–5.31; $P = 0.506$) were not associated with Len/Dex response. The multivariate analysis demonstrated similar results; age (HR: 1.04; 95% CI: 0.97–1.11; $P = 0.310$), sex (HR: 0.50; 95% CI: 0.18–1.40; $P = 0.190$), PFS by bortezomib-based induction therapies ≥18 months (HR: 1.79; 95% CI: 0.64–5.01; $P = 0.266$), auto-HSCT (HR: 2.18; 95% CI: 0.56–8.55; $P = 0.262$), and high-risk cytogenetics (HR: 0.85; 95% CI: 0.18–3.93; $P = 0.835$) were not significantly associated with depth of Len/Dex treatment.

Importantly, both the univariate (HR: 1.26; 95% CI: 0.49–3.26; $P = 0.628$) and multivariate (HR: 1.29; 95% CI: 0.43–3.88; $P = 0.648$) analyses failed to show that Len/Dex treatment would be more effective to relapsed MM patients treated

Table 2: Comparison of outcomes between symptomatic and biochemical relapsed myeloma patients treated with lenalidomide and dexamethasone

	All patients ($n=38$)	Symptomatic relapse ($n=10$)	Biochemical relapse ($n=28$)	*P*
Best response by Len/Dex, *n* (%)				
CR	3 (7.9)	1 (10.0)	2 (7.1)	0.964
VGPR	10 (26.3)	3 (30.0)	7 (25.0)	
PR	11 (28.9)	3 (30.0)	8 (28.6)	
SD	5 (13.2)	1 (10.0)	4 (14.3)	
Refractory disease	7 (18.4)	2 (20.0)	5 (17.9)	
Non-accessible	2 (5.3)	0	2 (7.1)	
Reasons for Len/Dex withdrawal, *n* (%)				
Progression	20 (69.0)	7 (87.5)	13 (61.9)	0.359
Refractory	6 (20.7)	1 (12.5)	5 (23.8)	
Adverse events	3 (10.3)	0	3 (14.3)	
Cytogenetic abnormality, *n* (%)				
del(17p)	4 (10.5)	0	4 (14.3)	0.556
del(13q)	12 (31.6)	3 (30.0)	9 (32.1)	1.000
t(11; 14)	2 (5.3)	0	2 (7.1)	1.000
t(4; 14)	2 (5.3)	0	2 (7.1)	1.000
t(14; 16)	0	0	0	

All data were compared between symptomatic and biochemical relapse groups by using the Chi-square test. Len/Dex: Lenalidomide and dexamethasone, CR: Complete remission, VGPR: Very good partial response, PR: Partial response, SD: Stable disease

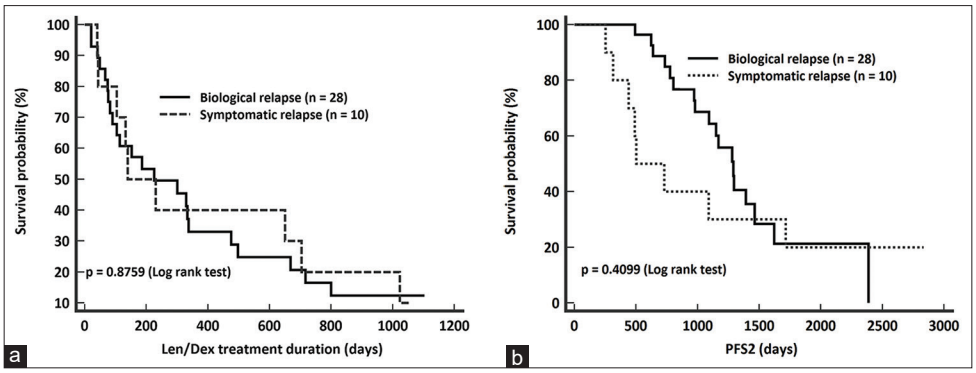

Figure 1: A comparison of Len/Dex treatment duration and PFS2 between the study groups. (a) The median Len/Dex treatment duration for patients treated for symptomatic relapse and biological relapse was 139 and 225 days, respectively ($P = 0.876$). (b) The median PFS2 in the symptomatic relapse group and biological relapse group was 501 and 1289 days, respectively ($P = 0.410$). Len/Dex: Lenalidomide and dexamethasone, PFS2: Progression-free survival 2.

Table 3: Factors associated with lenalidomide and dexamethasone treatment response*

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.01	0.97-1.06	0.563	1.04	0.97-1.11	0.310
Sex (male vs. female)	0.69	0.30-1.61	0.396	0.50	0.18-1.40	0.190
PFS by first induction therapy (≥18 months vs. <18 months)	1.67	0.67-4.18	0.270	1.79	0.64-5.01	0.266
Auto-HSCT (yes vs. no)	1.14	0.49-2.64	0.767	2.18	0.56-8.55	0.262
Types of relapse (biological vs. symptomatic relapse)	1.26	0.49-3.26	0.628	1.29	0.43-3.88	0.648
High-risk cytogenetics (yes vs. no)**	1.53	0.44-5.31	0.506	0.85	0.18-3.93	0.835

*Len/Dex treatment response indicates complete response, very good partial response, and partial response, **High-risk cytogenetics indicates del(17p), t(4; 14), and t(14; 16). Len/Dex: Lenalidomide and dexamethasone, PFS: Progression free survival, Auto-HSCT: Autologous hematopoietic stem cell transplantation, HR: Hazard ratio, CI: Confidence interval

for biological relapse than those treated for symptomatic relapse [Table 3].

Adverse events

In the current study, thrombocytopenia was the most common hematological adverse event, accounting for 15.8% (6/38). For non-hematological adverse events, skin rash was the highest (10.5%, 4/38) [Table 4]. Only three patients withdrew from Len/Dex treatment due to the adverse events in this study. Notably, patients receiving Len/Dex treatment for symptomatic relapse and biological relapse had similar reasons to withdraw from Len/Dex ($P = 0.359$). In the biological relapse group, 14.3% (3/28) of patients withdrew from Len/Dex due to adverse events. However, none of the patients in the symptomatic relapse group stopped Len/Dex treatment due to intolerable adverse events [Table 2].

Discussion

The current study demonstrated the cytogenetic features in relapsed MM patients previously treated by bortezomib-based induction therapy. Our study also showed that MM patients undergoing Len/Dex to treat biological relapse and symptomatic relapse had a similar treatment duration and PFS2. Neither high-risk cytogenetics nor biological or symptomatic relapse was attributed to the Len/Dex treatment response in these patients.

The reported distribution of high-risk cytogenetic abnormalities in RRMM varies in different studies. Yoshida *et al*.[16] showed 24.1%, 19.2%, and 8.4% of RRMM patients harbored t(11; 14), t(4; 14), and t(14; 16), respectively. However, this result was not entirely consistent with our findings. Our study revealed that only 10.6% of MM patients who had relapsed from bortezomib-based induction therapy had t(11; 14) or t(4; 14). Moreover, none of our study cohort had t(14; 16). On the contrary, del(17p) and del(13q) were identified among 10.5% and 31.6% of our patients, respectively. Numbers of prior treatments could be one of the reasons; more than half of the study cohort of Yoshida *et al*.[16] received at least two previous therapies before Len/Dex. Therefore, exposure to more prior therapies might induce more cytogenetic abnormalities. Besides, both relapsed and refractory MM patients were analyzed in Yoshida's cohorts. In contrast, we only examined cytogenetics by fluorescence *in situ* hybridization in patients who relapsed after bortezomib-based induction treatments in our study, which could be another reason for the inconsistency.

Our study also compared the outcomes among patients treated with Len/Dex for symptomatic relapse and biological relapse. Nozzoli *et al*.[17] showed that the median time to next treatment was significantly longer in MM patients with biological relapse than in patients with symptomatic relapse (34 vs. 19 months, $P < 0.008$). Furthermore, with a median PFS of

Table 4: Adverse events (*n*=38)

	All grades, *n* (%)	≥Grade 3, *n* (%)
Hematological adverse events		
Anemia	2 (5.3)	0
Leukopenia	1 (2.6)	0
Thrombocytopenia	6 (15.8)	2 (5.3)
Non-hematological events		
Skin rash	4 (10.5)	0
Fatigue	1 (2.6)	0
Peripheral neuropathy	1 (2.6)	0
Edema	1 (2.6)	0

24 vs. 13.2 months, Katodritou *et al*.[18] reported that patients treated for biological relapse had a significantly longer PFS than patients treated for symptomatic relapse (P = 0.006). However, whether a superior time to next treatment can translate into a better OS remains uncertain. Besides, not every patient has the chance to identify biological relapse before symptoms occur. This can result in a bias for PFS to be an outcome measure in this comparison. To avoid this bias, we used Len/Dex treatment duration and PFS2 to compare the outcome among patients treated for symptomatic and biological relapses. In our study, although patients treated for biological relapse had a more extended period of Len/Dex treatment than patients treated for symptomatic relapse, the difference was not significant (225 vs. 139 days; P = 0.876). Moreover, these two groups of patients had a comparable median PFS2, suggesting treating relapsed MM earlier might not always result in an increased OS time.

The depth of treatment response by Len/Dex could be one of the explanations for this conclusion. Depth of response is clinically relevant to OS in RRMM.[19] In our study, the best treatment response to Len/Dex was similar among patients treated for symptomatic and biological relapses (P = 0.964). Univariate (HR: 1.14; 95% CI: 0.49–3.26; P = 0.628) and multivariate (HR: 1.29; 95% CI: 0.43–3.88; P = 0.648) analyses further supported that symptomatic or biological relapse was not associated with the depth of Len/Dex treatment. A study by Jones *et al*.[20] reported that depth of response is a key determinant of the evolutionary patterns seen in relapsed MM. This result further explains why not the first PFS ≥18 months and high-risk cytogenetic features were associated with the Len/Dex treatment response in our study.

Small sample size and non-randomized study design were the significant limitations of this study. The OS was not analyzed because of a short follow-up time. Besides, we did not further stratify patients in the biological group into significant biological relapse and nonsignificant biological relapse due to the limited patient number.[13] In addition, the decision to use Len/Dex to treat symptomatic relapse or biological relapses was made by investigators or patients, which could result in patient selection bias.

Conclusion

In conclusion, our study demonstrated the cytogenetic features in MM relapsing from bortezomib-based induction treatments. Our data also showed that age, sex, high-risk cytogenetics, and longer PFS by bortezomib-based induction were not attributed to the depth of Len/Dex treatment. Whether MM patients treated by Len/Dex for biological relapse would have a better OS than those prescribed for symptomatic relapse is still inconclusive. Further prospective studies with larger cohorts and randomized study designs are needed to answer this question. Using Len/Dex to treat significant biological relapse and symptomatic relapse remains the current consensus.

Acknowledgments

This study was financially supported by grants from the Multiple Myeloma Working Group, Hematology Society of Taiwan.

Financial support and sponsorship

This study was financially supported by grants from the Multiple Myeloma Working Group, Hematology Society of Taiwan.

Conflicts of interest

There are no conflicts of interest.

References

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-60.
2. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, *et al*. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-17.
3. Cavo M, Pantani L, Pezzi A, Petrucci MT, Patriarca F, Di Raimondo F, *et al*. Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. Leukemia 2015;29:2429-31.
4. Holstein SA, Suman VJ, McCarthy PL. Update on the role of lenalidomide in patients with multiple myeloma. Ther Adv Hematol 2018;9:175-90.
5. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, *et al*. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.
6. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, *et al*. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.
7. Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, *et al*. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147-52.
8. Jo JC, Lee HS, Kim K, Lee JJ, Yoon SS, Bang SM, *et al*. The effectiveness and safety of lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma in real-world clinical practice: A study of the Korean Multiple Myeloma Working Party (KMMWP-151 study). Ann Hematol 2020;99:309-19.
9. Dimopoulos MA, Lonial S, White D, Moreau P, Palumbo A, San-Miguel J, *et al*. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol 2017;178:896-905.
10. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, *et al*. Daratumumab, lenalidomide, and dexamethasone for multiple

myeloma. N Engl J Med 2016;375:1319-31.
11. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, *et al*. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374:1621-34.
12. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, *et al*. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.
13. Ludwig H, Sonneveld P, Davies F, Bladé J, Boccadoro M, Cavo M, *et al*. European perspective on multiple myeloma treatment strategies in 2014. Oncologist 2014;19:829-44.
14. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, *et al*. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328-46.
15. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, *et al*. Revised international staging system for multiple myeloma: A report from international myeloma working group. J Clin Oncol 2015;33:2863-9.
16. Yoshida T, Ri M, Fujinami H, Oshima Y, Tachita T, Marumo Y, *et al*. Impact of chromosomal abnormalities on the efficacy of lenalidomide plus dexamethasone treatment in patients with relapsed/refractory multiple myeloma. Int J Hematol 2019;110:228-36.
17. Nozzoli C, Staderini M, Veltroni A, Longo G, Bacchiarri F, Donnini I, *et al*. Impact of disease status on outcome in relapsed and refractory multiple myeloma treated with lenalidomide. Leuk Lymphoma 2015;56:2388-91.
18. Katodritou E, Kyrtsonis MC, Delimpasi S, Kyriakou D, Symeonidis A, Spanoudakis E, *et al*. Real-world data on Len/Dex combination at second-line therapy of multiple myeloma: Treatment at biochemical relapse is a significant prognostic factor for progression-free survival. Ann Hematol. 2018;97:1671-82.
19. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, *et al*. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-66.
20. Jones JR, Weinhold N, Ashby C, Walker BA, Wardell C, Pawlyn C, *et al*. Clonal evolution in myeloma: The impact of maintenance lenalidomide and depth of response on the genetics and sub-clonal structure of relapsed disease in uniformly treated newly diagnosed patients. Haematologica 2019;104:1440-50.

Supplemental Table 1: Definitions of clinical and biological relapse

Clinical relapse
Development of new soft-tissue plasmacytomas or bone lesions
Definite increase in the size of existing plasmacytomas or bone lesions
Hypercalcemia (>11.5 mg/dL; 2.65 mmol/L)
Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L), because of myeloma
Rise in serum creatinine by 2 mg/dL or more (177 mmol/L or more), because of myeloma
Hyperviscosity requiring therapeutic intervention
Significant biochemical relapse in patients without clinical relapse (IMW Paris 2011)
Doubling of the M-component in two consecutive measurements separated by <2 months with the reference value of 5 g/L, or
In two consecutive measurements any of the following increases:
The absolute levels of serum M protein by ≥10 g/L, or
An increase of urine M protein by ≥500 mg per 24 hours, or
An increase of involved FLC level by ≥20 mg/dL (plus an abnormal FLC ratio) or 25% increase (whichever is greater)
Nonsignificant biochemical relapse
Biochemical relapse not meeting criteria of significant biochemical relapse

Source from: Ludwig *et al*.[13] IMW: International Myeloma Workshop, FLC: Free light chain