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Dose-adjustment of lenalidomide according to patient age and vulnerability is feasible in relapsed or refractory multiple myeloma: retrospective analysis of 20 cases

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ABSTRACT

The European Myeloma Network (EMN) has recently proposed an algorithm for the optimal starting dose and dose modification of antimyeloma drugs for elderly or unfit patients with multiple myeloma. However, the feasibility of this algorithm remains unclear. Therefore, we retrospectively assessed the feasibility of lenalidomide therapy for 20 patients with relapsed or refractory multiple myeloma (RRMM). We divided the patients into two groups, the recommended dose (RD) group (n = 12) in which the administered dose corresponded to the recommended dose according to the EMN algorithm, and the non-recommended dose (NRD) group (n = 8) in which the administered dose did not correspond to the recommended dose and we compared the efficacy and toxicity of lenalidomide therapy between the two groups. The overall response rate was 67% and 63% in the RD and NRD groups, respectively. There was no significant difference in time to progression between the two groups (9 vs. 14 months P = 0.75). Grade 3/4 neutropenia and grade 2/3 fatigue were less frequent in the RD group than in the NRD group (50% vs. 88% and 8% vs. 38%, respectively). The discontinuation rate due to severe adverse events was much lower in the RD group than in the NRD group (17% vs. 50%). These results indicated that the dose adjustment strategy of lenalidomide according to the algorithm may maintain efficacy and improve the safety profile in patients with RRMM. From our results, the algorithm seemed to be feasible for elderly or unfit myeloma patients in daily practice. A larger prospective study is needed to confirm the feasibility of this algorithm.

INTRODUCTION

Multiple myeloma is a neoplastic plasma cell disorder that is characterized by the clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood and urine, and associated organ dysfunction [1]. The median age at diagnosis is approximately 70 years;

26% are aged 65–74 years old, and 37% are older than 75 years [2]. In recent years, the introduction of novel agents such as thalidomide, lenalidomide (Len), and bortezomib has improved the overall survival of multiple myeloma (MM) [3, 4]. However, this improvement was mainly seen in younger patients, whereas it was modest or absent in elderly or very elderly patients [2, 3, 5]. A recent meta-analysis of data from 1685 untreated elderly patients in six randomized studies of melphalan in combination with prednisone (MP) versus MP plus thalidomide (MPT) showed better progression-free survival (PFS) and overall survival (OS) in the MPT group than in the MP group [6]. This improvement was also less pronounced in patients older than 75 years. In addition, some studies had reported a doubling of early toxic deaths among patients older than 75 years and no favorable effect of thalidomide on OS in patients with higher World Health Organization performance status [7, 8]. A meta-analysis of data from 1435 untreated elderly patients in four randomized studies of thalidomide and/or bortezomib showed that age ≥ 75 years, or renal failure at presentation, occurrence of infections, and cardiac or gastrointestinal adverse events negatively affected survival [9]. Many patients older than 75 years are vulnerable because of their comorbid conditions that can complicate the presentation and management of MM. Therefore, personalized therapy using dose-adjusted regimens is urgently needed for these patients.

The European Myeloma Network (EMN) has recently proposed an algorithm of starting dose and dose modification of antimyeloma agents according to patient age, vulnerability and non-hematologic adverse events [10]. However, the feasibility of this algorithm remains unknown. We, therefore, retrospectively assessed the feasibility of this algorithm for relapsed or refractory transplant-ineligible myeloma patients treated with Len in combination with or without dexamethasone (Dex) in our institution.

PATIENTS & METHODOLOGY

Patients

Data from 20 patients with relapsed or refractory MM (RRMM) who had received at least two cycles of Len with or without Dex between July 2010 and June 2012 (before the proposal of the EMN algorithm) in our institution were retrospectively analyzed.

Treatment dose and schedule

The treatment consisted of 28-day cycles of Len 15 or 25 mg/day (10 mg in case of renal impairment) on days 1–21, in combination with or without Dex at various dose levels. The starting doses and schedule of Len and Dex were modified at the physician's discretion.

Stratification of patients

Patients were retrospectively divided into two groups—the recommended dose (RD) and non-recommended dose (NRD) groups—according to whether the actual starting dose corresponded to the recommended dose by the EMN algorithm or not. To determine the recommended dose of Len, we investigated the risk factors including age, frailty, comorbidities, and adverse events, in each patient from medical records. For dose adjustment, EMN proposed the following risk factors: age ≥ 75 years, frailty, comorbidities, or any severe non-hematologic adverse events [10]. The recommended starting doses were as follows: no risk factors, 25 mg/day; at least one risk factor, 15 mg/day; and any grade 3/4 non-hematologic adverse events, administration of lower doses of Len at the next cycle. The RD group was defined as the patients in whom the actual dose of Len corresponded to the recommended dose. The NRD group was defined as the patients in whom the actual dose of Len did not correspond to the recommended dose and/or in whom the dose of Len was not reduced at the next cycle despite the presence of severe non-hematologic adverse events. Fisher's exact or Chi-square test was used to analyze intergroup differences in the following: sex, M protein class, international staging system (ISS), and previous treatment with novel agents. In addition, intergroup differences in age, lines of prior treatment, and administered doses of Len and Dex were analyzed using t-test.

Safety and efficacy

To assess the feasibility of the algorithm, we compared four parameters between the two groups: discontinuation rates of Len, response rate, time to progression (TTP), and toxicities. The response rate was assessed using the International Myeloma Working Group (IMWG) uniform response criteria [11]. TTP was defined as

the duration from the start of treatment with Len to progressive disease. TTP was calculated using the Kaplan–Meier method and intergroup differences were compared using the log-rank test. Adverse events were graded by the Common Terminology Criteria, which were proposed by the National Cancer Institute (version 4.0).

RESULTS AND OBSERVATIONS

Patients

Patients and clinical characteristics are shown in Table 1. The median age was 72 years. The daily starting doses of Len were 25 mg in 11 patients (55%), 15 mg in 7 (35%), and 10 mg in 2 (10%). The RD and NRD groups had 12 and eight patients, respectively. The median age was nonsignificantly higher in the NRD group than in the RD (75 vs. 70 years). Paraprotein types, clinical stages, and the median lines of previous treatment were comparable between the two groups. In the RD group, 4 patients (33%) were treated with Len at 25 mg as a daily starting dose, 6 (50%) at 15 mg, and 2 (17%) at 10 mg. In contrast, 7 (87%) of 8 patients in the NRD group were treated with Len at 25 mg. The mean starting dose of Dex per cycle was also higher in the NRD group than in the RD group (258 mg vs. 180 mg), but the difference was not significant.

Table 1. Clinical characteristics according to lenalidomide dose group

Characteristics	All patients (n = 20), n (%)	Recommended dose group (n = 12), n (%)	Non-recommended dose group (n = 8), n (%)	P value
Age (Median, range)	72 (58–83)	70 (60–83)	75 (58–79)	.88
≤ 65	6 (30)	4 (33)	2 (25)	
65–75	6 (30)	4 (33)	2 (25)	
> 75	8 (40)	4 (33)	4 (50)	
Sex (M/F)	12 (60) 8 (40)	11 (92) 1 (8)	2 (25) 6 (75)	< .01
M-Protein Class				.50
IgG	12 (60)	6 (50)	6 (75)	
IgA	3 (15)	2 (17)	1 (13)	
Bence Jones protein	5 (25)	4 (33)	1 (13)	
ISS				.53
1–2	9 (45)	8 (67)	2 (25)	
3	4 (20)	2 (17)	2 (25)	
Median lines of prior Tx (range)	3 (1–5)	3 (1–5)	3 (2–3)	.85
Prior Tx with				1.0
Bortezomib	16 (80)	8 (67)	8 (100)	
Thalidomide	2 (10)	1 (8)	1 (13)	
Starting dose of lenalidomide				.01
25 mg	11 (55)	4 (33)	7 (87)	
15 mg	7 (35)	6 (50)	1 (13)	
10 mg	2 (10)	2 (17)		
Mean starting dose of dexamethasone per cycle	219 mg	180 mg	258 mg	.41

Four (20%) patients received Len monotherapy. The patients' ages, frailty status, comorbidities, and doses of Len are summarized in Table 2. In the RD group, 4 (33%) of 12 patients were older than 75 years, 3 had mild frailty, and 5 had comorbidities that included renal impairment, neurogenic bladder, chronic obstructive pulmonary disease, and mental disorders. In the NRD group, 4 (50%) of 8 patients were older than 75 years, 4 had mild to severe frailty, and 2 had comorbidities such as mental and cardiac disorders. Despite the fact that 7 of 8 patients had at least one risk factor, the full dose of Len (25 mg) was given as a starting dose, and although one patient received the recommended dose (15 mg), the dose was not reduced to a lower dose level (10 mg) for the next cycle despite the occurrence of a severe non-hematologic adverse event.

Table 2. Risk factors and lenalidomide doses of 20 patients

	Age	Frailty	Comorbidities	Recommended dose (mg)	Actual dose (mg)
Recommended dose group					
1	78*	Mildly frail*		15	15
2	69	Very fit		25	25
3	64	Very fit		25	25
4	60	Moderately fit		25	25
5	72	Vulnerable		25	25
6	65	Vulnerable	Renal impairment*	10	10
7	63	Mildly frail*		15	15
8	77*	Vulnerable	Renal impairment*	10	10
9	71	Moderately fit	Neurogenic bladder*	15	15
10	83*	Mildly frail*		15	15
11	80*	Moderately fit	Pulmonary disorder*	15	15
12	68	Moderately fit	Mental disorder*	15	15
Non-recommended dose group					
1	77*	Vulnerable		15	25
2	58	Mildly frail*	Mental disorder*	15	25
3	77*	Moderately frail*	Cardiac disorder*	15	25
4	79*	Moderately fit		15	25
5	74	Moderately frail*		15	25
6	76*	Vulnerable		15	25
7	72	Moderately frail*		15→10	15→15**
8	58	Mildly frail*		15	25

* Risk factor, ** Lenalidomide was not restarted at a lower dose despite grade 3 non-hematologic adverse event appeared

Table 3. Adverse events in 20 patients according to the doses of lenalidomide

	RD N (%)		NRD N (%)	
Hematological AE	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	4 (33.3)	2 (16.7)	5 (62.5)	2 (25.0)
Anemia	1 (8.3)	0 (0.0)	1 (12.5)	0 (0.0)
Thrombocytopenia	1 (8.3)	1 (8.3)	0 (0.0)	1 (12.5)
Non-hematological AE	Grade 2	Grade 3	Grade 2	Grade 3
Edema	1 (8.3)	0 (0.0)	1 (12.5)	0 (0.0)
Peripheral neuropathy	3 (25.0)	0 (0.0)	2 (25.0)	0 (0.0)
Fatigue	1 (8.3)	0 (0.0)	2 (25.0)	1 (12.5)
Myalgia	1 (8.3)	1 (8.3)	0 (0.0)	2 (25.0)
Cutaneous toxicity	1 (8.3)	1 (8.3)	1 (12.5)	0 (0.0)
Infection	1 (8.3)	2 (16.7)	1 (12.5)	1 (12.5)

Adverse events

We observed transient and manageable hematological toxicities in both groups (Table 3). Six (50%) patients of the RD group and 7 (87.5%) of the NRD group had grade 3/4 neutropenia, which were resolved by drug interruption and G-CSF support. The grade 3/4 infection rate was comparable between the groups. In terms of non-hematological toxicities, grade 2 or 3 fatigue and myalgia were more commonly seen in the NRD group compared to the RD group.

Discontinuation of treatment

As shown in Table 4, the median follow-up time and treatment cycles were comparable between the two groups. The discontinuation rate due to any cause was also comparable between the RD and NRD groups (50% vs. 62.5%). However, the discontinuation rate due to severe adverse events was much higher in the NRD group than in the RD group (50% vs. 17%). In addition, the mean actual administered daily dose of Len was similar between both groups (15.7 vs. 18.8 mg).

Table 4. Discontinuation of treatment and mean administered dose of lenalidomide according to the starting dose

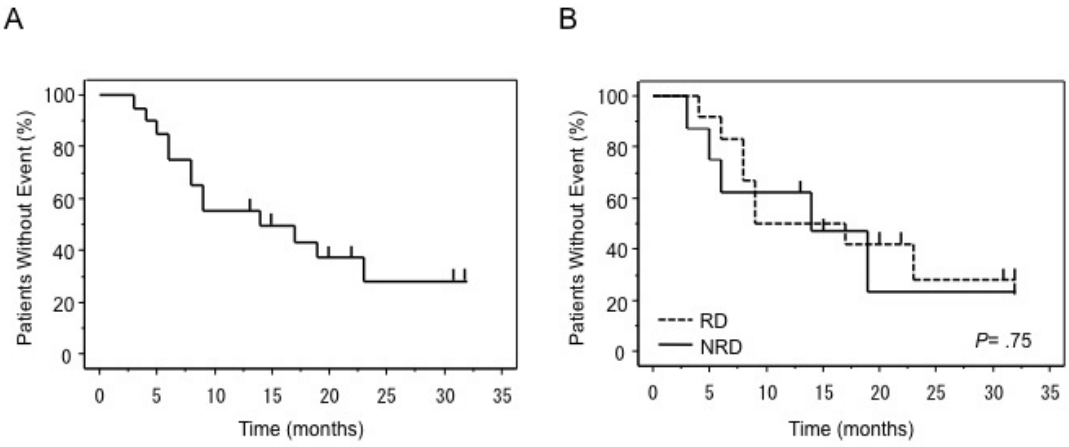
	All patients (n = 20)	RD (n = 12)	NRD (n = 8)
Median follow-up time (month) (range)	15 (2–35)	14 (2–32)	15 (2–32)
Median cycles (range)	12 (2–35)	14 (2–32)	12 (2–31)
Discontinuation, n (%)	11 (55)	6 (50)	5 (62.5)
Discontinuation due to AE, n (%)	6 (30)	2 (17)	4 (50)
Mean administered dose of lenalidomide (mg/day)	17.3	15.7	18.8

Response to treatment

Of the 12 patients in the RD group, two (16.7%) achieved a (immunofixation-negative) complete response (CR), one (8.3%) achieved a very good partial response (VGPR), and five (41.6%) achieved a PR; this resulted in an overall response rate (ORR) (≥ PR) of 66.7%. Of the eight patients in the NRD group, three (37.5%) achieved a VGPR and two (25%) achieved a PR, which resulted in an ORR of 62.5%. The median TTP was 14 months in all patients, at 9 in RD, and 14 in the NRD group (Figure 1). However, there was no significant difference in TTP between both groups (P = 0.75).

Figure 1. Time to progression

(A) TTP in all patients. (B) TTP in the recommended dose and non-recommended dose groups. RD; recommended dose group, NRD; non-recommended dose group.



DISCUSSION

Our analysis retrospectively evaluated the feasibility of dose modification of Len according to the EMN algorithm for unfit patients with RRMM. Severe neutropenia was more frequently observed in the NRD group than in RD group (87.5% vs. 50%, Table 3). In addition, grade 3/4 infection was seen in 25% of the patients in each group. This may be due to not only neutropenia but also the use of a higher dose of Dex (>160 mg/cycle). Indeed, the frequency of neutropenia in our series seemed to be higher than previous reports. Quach et al reported on the statistical comparison of the efficacy and safety of low-dose Len plus Dex (RevLite study) with full-dose Len plus Dex (MM-009/010 study) in RRMM [12]. In the report, severe neutropenia was seen in 27% and 41% of the RevLite and MM-009/010 studies, respectively. On the other hand, Iida et al reported that grade 3 or 4 neutropenia was observed in 67% at the interim analysis for a prospective study for Japanese RRMM patients treated with either Len (10 mg or 25 mg/day) alone or in combination with Dex [13]; this result together with ours indicates the possibility of higher incidence rates of severe neutropenia in Japanese patients than in Caucasian patients. The other possibilities may be a higher proportion of elderly and unfit patients in our series. However, patients older than 65 years were comparable among our study, the RevLite and the MM-

009/010 trials (70% vs. 71% vs. 63%, respectively) [14]. These observations suggested that the high frequency of severe neutropenia in our series may be due to racial differences, a higher inclusion of unfit patients, and the study with a small number of patients. Thus, we should be aware of the potential of severe neutropenia and infection even in patients who received lower doses of Len, and modify the dose of not only Len but also Dex according to the algorithm.

Non-hematological toxicity such as fatigue and myalgia was less frequent in the RD group than in the NRD group, indicating that dose-adjusted treatment of Len improved the safety profile of non-hematological toxicity. Interestingly, the mean administered daily dose of Len in the RD group was similar to that in the NRD group (15.7 mg vs. 18.8 mg) although 7 of 8 patients in the NRD group were initially treated with a full dose of Len (25 mg/day); this suggested that dose reduction was more frequent in the NRD group because of toxicity. Drug discontinuation due to adverse events was associated with a shorter survival, probably because of a lower cumulative delivered dose. Palumbo et al reported that the outcomes of patients aged 75 years or over who received melphalan, prednisone, and Len were worse than younger patients, due to the higher discontinuation rate and subsequent lower cumulative dose intensity of both melphalan and Len [14]. Moreover, Mateos et al showed that a once-weekly schedule of bortezomib significantly reduced the incidence of severe hematologic and non-hematologic adverse events and the rate of drug discontinuation without having a negative impact on outcome [15]. These findings indicated that it was important to maintain efficacy to avoid drug discontinuation and to deliver the appropriate dose intensity. In our study, the discontinuation rate due to adverse events was lower in the RD group than in the NRD group (17% vs. 50%), indicating that the starting dose modification of Len according to the EMN algorithm improved the safety profile in unfit patients.

In our analysis, the ORR was comparable between the two groups (67% vs. 63%). The efficacy was also compatible with previous studies. In the MM-009/010 and RevLite studies, ORR was 60% and 69%, respectively [12]. TTP was comparable between the RD and NRD groups (9 vs. 14 months, P = 0.75) in our series. These observations suggested that the dose modification strategy maintained the efficacy in unfit patients with RRMM. A prospective study will be needed to evaluate the impact of this strategy on TTP because we used a retrospective study with small number of patients and short-term follow-up in our study.

A meta-analysis of several trials for elderly patients showed that the achievement of CR translated to survival benefit [16]. However, it will be necessary to pay attention when applying the evidence to clinical practice because clinical trials are strict about patient selection. In addition, intensified regimes including novel agents have had unfavorable outcomes in very elderly patients because of treatment-related toxicities [7]. Thus, patient-tailored therapy using dose modification of antimyeloma drugs may be recommended in elderly and/or unfit patients to minimize toxicity and maintain efficacy, as well as to avoid undertreatment in fit patients.

CONCLUSION

The starting dose modification of Len according to the EMN algorithm seems to be feasible for transplantation-ineligible patients with RRMM. Prospective feasibility studies are warranted.

LIST OF ABBREVIATIONS

EMN – European Myeloma Network

RRMM – relapsed or refractory multiple myeloma

MM – multiple myeloma

RD – recommended dose

NRD – non-recommended dose

Len – lenalidomide

MP – melphalan plus prednisone

MPT – MP plus thalidomide

PFS – progression-free survival

OS – overall survival

Dex – dexamethasone

ISS – international staging system

TTP – time to progression

IMWG – International Myeloma Working Group

CR – complete response

VGPR – very good partial response

ORR – overall response rate

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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