Efficacy of Lenalidomide plus Low-Dose Dexamethasone in Thai Patients with Relapsed and/or Refractory Multiple Myeloma

Chutima Kunacheewa, M.D., Noppadol Siritanaratkul, M.D.

Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok 10700, Thailand.

ABSTRACT

Objective: Lenalidomide is an immunomodulatory agent with proven efficacy in the treatment of multiple myeloma. In large global clinical studies, lenalidomide plus dexamethasone has demonstrated significant improvements in the overall response rate and overall survival in patients with relapsed and/or refractory multiple myeloma, compared with a placebo and dexamethasone. This is the first study to report lenalidomide plus low-dose dexamethasone administered in Thai patients.

Methods: The aim of this phase II, single-center, single-arm study was to evaluate the efficacy and safety of lenalidomide and low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. The primary endpoint was the overall response rate at the fourth treatment cycle. Secondary endpoints included depth of response, time to response, and adverse events.

Results: In total, 15 patients with a median age of 61 years old (range 23-74 years old) who had received at least one prior anti-myeloma therapy were enrolled in the study and administered 4-week cycles of lenalidomide 25 mg/day (days 1-21) and dexamethasone 40 mg/week. Patients continued in the study until the occurrence of disease progression or serious adverse events. The overall response rate was 86% and 73.3% at the fourth and from all treatment cycles, respectively (median number of treatment cycles, 10.25), and the median dose for patients aged >60 years old was 15 mg/day. The overall response rate at the fourth cycle in patients who had received prior novel agents (bortezomib and/or thalidomide) was 81.82% compared with 100% in those who had received prior conventional therapy ($p = 0.15$). The most common adverse events reported were anemia and neutropenia, which were both manageable.

Conclusion: Lenalidomide and low-dose dexamethasone was highly effective in Thai patients with relapsed and/or refractory multiple myeloma, with a manageable adverse event profile. These findings suggest that lenalidomide 15 mg/day is a safe and effective dose for Thai patients aged ≥60 years old.

Keywords: Relapsed multiple myeloma; refractory multiple myeloma; lenalidomide; adverse events (Siriraj Med J 2021; 73: 344-353)

INTRODUCTION

Multiple myeloma is a plasma cell disorder that, to date, remains incurable.[1] Patients with relapsed and treatment-refractory multiple myeloma require effective salvage therapies to prolong disease-free progression. The introduction of autologous stem cell transplantation, and newer agents for the treatment of multiple myeloma, has substantially improved the options available for

Corresponding Author: Noppadol Siritanaratkul
E-mail: sinoppadol@gmail.com
Received 29 May 2020 Revised 4 January 2021 Accepted 6 January 2021
ORCID ID: http://orcid.org/0000-0001-8624-5516
http://dx.doi.org/10.33192/Smj.2021.45

patients who do not respond well to initial therapy. Novel agents including immunomodulatory drugs (thalidomide, lenalidomide), proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), and monoclonal antibodies (elotuzumab and daratumumab) in combination with other agents have all demonstrated favorable results in terms of response, progression-free survival, and also overall survival, compared to established treatments for refractory disease, such as melphalan-based regimens or alkylating agents.[1-4]

Currently, worldwide practice uses a combination of newer novel agents, such as carfilzomib/lenalidomide/dexamethasone, daratumumab/lenalidomide/dexamethasone, or elotuzumab/lenalidomide/dexamethasone, in relapsed refractory multiple myeloma.[2-4] However, in Thailand, economic limitations have led to these new novel agents being generally unavailable for this group of patients. Although, lenalidomide plus dexamethasone has been a standard treatment in Western countries in the past decade, for developing countries, like Thailand, this combination only now represents a new hope for myeloma patients.

In phase III clinical trials (MM-009[5], MM-010[6], the use of lenalidomide plus dexamethasone in relapsed/refractory multiple myeloma patients produced improvements in overall survival and event-free survival compared with high-dose dexamethasone alone.[5,6] However, in these and other studies, lenalidomide was shown to be associated with a higher rate of grade 3-4 hematologic toxicity and a high incidence of thromboembolic events compared with dexamethasone alone.[5-7] In a randomized, controlled trial of patients with newly diagnosed multiple myeloma, the combination of lenalidomide with either high- or low-dose dexamethasone as an initial therapy resulted in high rates of treatment response and event-free survival.[8] Lenalidomide with low-dose dexamethasone was associated with significantly higher rates of overall survival at 1 year, and lower rates of thromboembolic events than lenalidomide with high-dose dexamethasone.[6-8]

There are few published data on the efficacy and safety of lenalidomide in the treatment of refractory/relapsed multiple myeloma patients in Asia. This study is the first to prospectively evaluate the administration of lenalidomide for multiple myeloma in Thailand. The aim of the study was to investigate the efficacy and safety of lenalidomide plus low-dose dexamethasone in Thai patients with refractory/relapsed multiple myeloma.

MATERIALS AND METHODS

Patients

Patients were eligible for inclusion in the study if aged ≥18 years old and if they presented with progressive multiple myeloma after at least one previous treatment regimen (e.g., vincristine, adriamycin, dexamethasone [VAD]; liposomal doxorubicin, vincristine, dexamethasone; high-dose dexamethasone; cyclophosphamide plus dexamethasone; cyclophosphamide plus prednisolone; bortezomib plus dexamethasone [VD]; thalidomide plus dexamethasone; thalidomide, cyclophosphamide, dexamethasone; bortezomib, thalidomide, dexamethasone; VD plus panobinostat; dexamethasone, cyclophosphamide, etoposide, cisplatin [DCEP]; or melphalan plus prednisolone).[9,10] Patients were required to have adequate hematologic and organ function, as demonstrated by an absolute neutrophil count ≥1,500/μL, platelet count ≥75,000/μL, hemoglobin ≥7.5 g/dL, serum creatinine <2.0 mg/dL, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels <3x the upper limit of normal, all obtained 21 days prior to enrolment. Additionally, patients were eligible for the study if they had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Women with childbearing potential were eligible if they agreed to use contraception and had a negative pregnancy test before enrolment and took monthly pregnancy tests thereafter. Exclusion criteria for this study were dexamethasone intolerance or an allergy to any of the study mediations; inadequate liver or renal function at screening; ≥grade 2 peripheral neuropathy within 14 days prior to screening; the diagnosis or treatment of another malignancy within 2 years prior to screening (with the exception of patients with non-melanoma skin carcinoma who had undergone complete resection); ongoing or active hepatitis B virus , hepatitis C virus or HIV infection; uncontrolled comorbid cardiovascular conditions within 6 months prior to screening; an inability to take oral medication, or unwillingness to comply with the drug administration requirements, or have undergone a gastrointestinal procedure that could interfere with oral absorption or tolerance of treatment; and pregnancy. This study was approved by the Ethics Review Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University (Si 650/2010).

Study design

This was a phase II, single-center, single-arm, open-label study. Patients received oral lenalidomide 25 mg/day on days 1–21 of a 28-day cycle and dexamethasone 40 mg once weekly. The lenalidomide dose was adjusted according to patients' creatinine clearance level, absolute neutrophil count, and platelet count as recommended by the European Myeloma Network.[11] Treatment was continued until disease progression, as defined below.

Thromboembolic prophylaxis with aspirin 81 mg daily was administered to patients with at least one risk factor for thrombosis according to the International Myeloma Working Group (IMWG) guidelines for the prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.[12]

Complete blood count, blood chemistry and physical examination were conducted every 15 days in the first treatment cycle and every 4 weeks thereafter.

Response criteria

Patient disease response and progression were assessed according to the IMWG guidelines[10] and the European Group for Blood and Marrow Transplant[9] criteria for multiple myeloma. A partial response was defined as a reduction of M protein by at least 50% in the serum and 90% in urine, or both.[9,10] A complete response was defined as the complete disappearance of M protein in serum and urine by immunofixation and <5% plasma cell presence in the marrow. A very good partial response (VGPR) was defined as a >90% reduction of M protein in the serum and urine.[9,10] In patients with light chain MM, the IMWG 2011 response criteria was used. A >90% reduction of difference in involved and uninvolved serum FLC was classified as VGPR and the CR criteria require a normal serum FLC ratio in addition to CR criteria defined above.[13]

Progressive disease was defined as a ≥25% increase in serum M protein from best response, or an absolute increase in serum M protein of >500 mg/dL compared to the nadir value, or the appearance of a new bone lesion or plasmacytoma that was increasing in size.[9,10]

All toxicities were graded and attributed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.

Statistical analysis

The primary endpoint was the overall response rate (ORR) at the end of the fourth treatment cycle. Secondary endpoints included response to therapy across all cycles (limited to eight cycles), toxicity, dose adjustment due to toxicity, and time to progression (TTP). Descriptive continuous data were summarized using mean (SD), median (range) according to their distribution and categories data were demonstrated as percentage. Response to therapy was evaluated using the chi-square test to compare treatment response between patients who did or did not receive novel agents prior to enrolment. The Mann–Whitney test was used to compare the appropriate lenalidomide dose (the mean effective dose following adjustment for adverse events) in patients aged <60 and ≥60 years old. All patients were included for analysis ORR and toxicities.

RESULTS

Patient characteristics

In total, 15 patients were enrolled in this study between January 2011 and March 2012 at Siriraj Hospital, Bangkok. The median age was 61 years old (range 23-74 years old). Among these patients, 11 had received a novel agent in a prior treatment regimen, with a median of two prior treatment regimens (range 1-7). Other baseline characteristics and laboratory findings are summarized in Tables 1 and 2, respectively.

Treatment administration

Patients received a median of 10.25 treatment cycles (range 1.8-15); nine received eight complete cycles and were eligible for evaluation in this study. Two patients progressed before the fourth treatment cycle (1 of 2 them previously underwent transplantation) and were excluded from the study to receive another salvage therapy; two patients progressed at the fifth and seventh cycles, respectively, after achieving a partial response at the fourth cycle; one of these patients died as a result of infection without neutropenia after achieving a very good partial response at the fourth cycle. Two patients underwent autologous stem cell transplantation after achieving a complete response. Fig 1 illustrates the treatment pathway of the enrolled patients.

The lenalidomide dose was adjusted according to toxicity. In total, 105 doses of lenalidomide were administered. Nine of the 15 patients received a reduced lenalidomide dose, as shown in Table 2. The median lenalidomide dose was 25 mg for patients aged ≤60 years old and 15 mg for patients >60 years old (p = 0.101) (Table 3).

Aspirin 81 mg/day was administered as thromboprophylaxis for two patients (one patient with diabetes mellitus, and one patient who was immobilized due to plasmacytoma-related spinal cord compression) for the duration of lenalidomide therapy, when their platelet count was >50,000 µL. Another patient who developed bilateral edema in the legs after one cycle of lenalidomide treatment also started aspirin 81 mg/day, but this was stopped when no deep vein thrombosis was detected by compression ultrasonography. However, after complete 8 cycles of the treatment, all patients who had continued the treatment received aspirin 81 mg/day.

TABLE 1. Patient demographics and clinical characteristics at baseline.

Characteristic	All patients (n = 15) N (%)
Age (years); Median (min–max)	61 (23–74)
Gender: Male	5 (33)
ISS staging	
I	1 (20)
III	4 (80)
M protein isotype	
Immunoglobulin G	7 (47)
Immunoglobulin A	2 (13)
Light chain	6 (40)
Plasmacytoma	
Present	2 (13)
Number of previous treatment regimens	
Median (min–max)	2 (1–7)
Prior regimen	
Bortezomib	10 (67)
Thalidomide	7 (47)
Novel agent (bortezomib and/or thalidomide)	11 (73)
Stem cell transplantation	1 (7)
Laboratory	
Hemoglobin, g/dL; Median (min–max)	10.1 (7.5–11.9)
Creatinine, mg/dL; Median (min–max)	0.9 (0.5–1.8)
LDH, U/L; Median (min–max)	383 (227–864)
β-2-microglobulin, mg/L; Median (min–max)	4.75 (2.28–19.3)

Abbreviations: ISS, international staging system; LDH, lactate dehydrogenase.

TABLE 2. Lenalidomide-dose adjustment during the study.

Reasons for dose adjustment	n (%)
No. cycles administered	105
No. dose-adjusted cycles	14 (13.3)
No. patients with dose reduction (%)	9 (60)
Reason for dose reduction, n (%)	
Constitutional symptoms	4 (44.4)
Neutropenia	3 (33.3)
Renal insufficiency	3 (33.3)
Infection	2 (22.2)
Anemia	1 (1.1)
Thrombocytopenia	1 (1.1)

TABLE 3. Lenalidomide-dose adjustment according to patient age.

	Lenalidomide dose (mg/day)		
	≤60 years old	>60 years old	*p* value
Median (min–max)	25 (15–25)	15 (7.5–25)	0.101

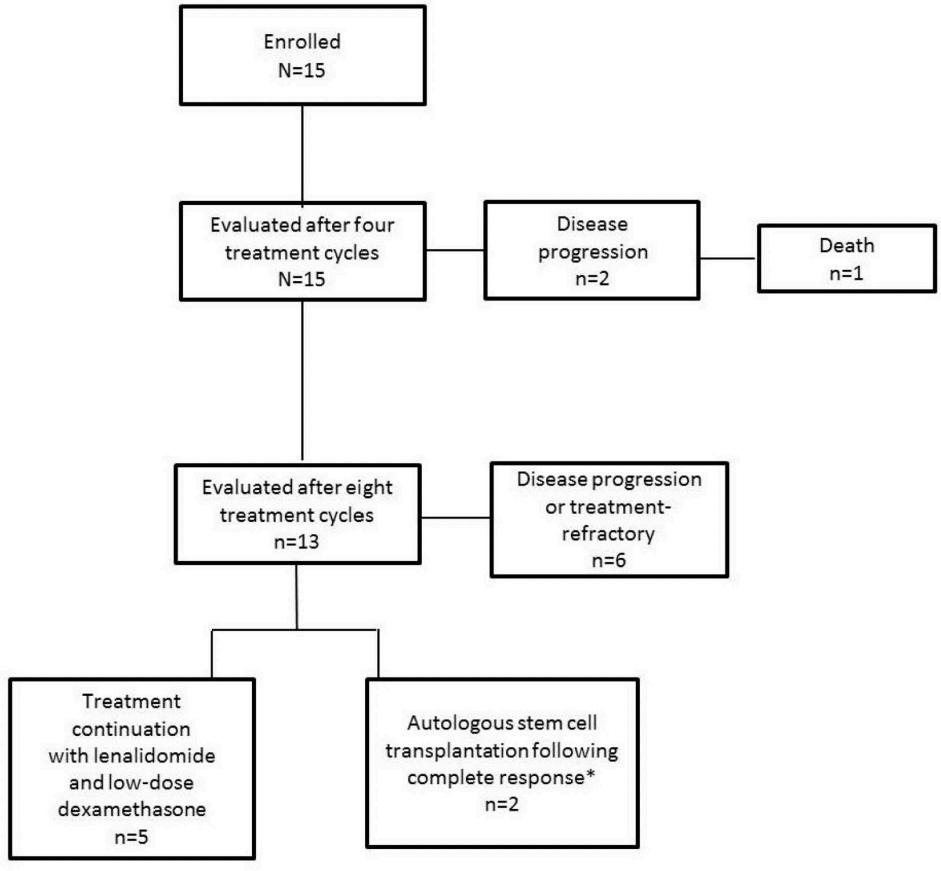


Fig 1. Treatment pathway and progression of patients during the study

Response to treatment

The median follow-up to treatment was 41 weeks (range 7-60 weeks). The ORR was 86% and 73.3% at the fourth treatment cycle and from all cycles, respectively. Seven patients (46.7%) achieved at least a very good partial response (VGPR) to treatment (Table 4). The ORR of patients with prior regimen ≤2 was trend to be better than those who received >2 prior line of therapy, 62% versus 39%, p=0.065. The ORR in patients who had received prior bortezomib or thalidomide compared with those who had not received prior novel therapy was 81.82% versus 100% (p = 0.15) and 63.6% versus 100% (p = 0.13) at the fourth and from all cycles, respectively (Table 5). The median time to response in patients who achieved a response was 0.93 months (range 0.93–2.8).

To date, five patients continue to receive lenalidomide with low-dose dexamethasone. Of the remaining patients, two underwent autologous stem cell transplantation, one patient died from septic pneumonia without neutropenia, two patients were refractory to this regimen, and five patients were considered to have progressive disease. The median time to progression (TTP) for these seven treatment-refractory patients was 8.9 months (range 1.8-14 months).

TABLE 4. Treatment response after four treatment cycles, and after all cycles.

Response	All patients (n = 15)		Prior bortezomib and/or thalidomide (n = 11)		Prior bortezomib (n = 10)		Prior thalidomide (n = 7)	
	Fourth treatment cycle	All cycles	Fourth treatment cycle	All cycles	Fourth treatment cycle	All cycles	Fourth treatment	All cycles cycle
ORR, n (%)	13 (86.7)	11 (73.3)	9 (81.8)	7 (63.6)	8 (77.8)	6 (60.0)	5 (71.4)	4 (57.1)
CR, n (%)	1 (6.7)	4 (26.7)	0	1 (9.1)	0	1 (10)	0	0
VGPR, n (%)	7 (46.7)	6 (40.0)	4 (36.4)	5 (45.5)	3 (30)	4 (40)	2 (28.6)	3 (42.9)
PR, n (%)	5 (33.3)	1 (6.7)	5 (45.5)	1 (9.1)	5 (50)	1 (10)	3 (42.9)	1 (14.3)
PD, n (%)	2 (13.3)	4 (26.7)	2 (18)	4 (36.4)	2 (20)	4 (40)	2 (28.6)	3 (42.9)

Abbreviations: CR, complete response; ORR, Overall response rate; PR, partial response; PD, progressive disease; VGPR, very good partial response

TABLE 5. Comparison of treatment responses between patients who received novel agents and those who received conventional therapy prior to lenalidomide administration.

Treatment group	Overall response rate per treatment group, n (%)			
	Fourth cycle (n = 15)	*p* value	All cycles* (n = 13)	*p* value
No prior bortezomib or thalidomide therapy	4 (100)	0.15	4 (100)	0.13
Prior bortezomib or thalidomide therapy	9 (81.8)		7 (63.6)	
No prior bortezomib only	5 (100)	0.08	5 (100)	0.15
Prior bortezomib only	8 (80)		6 (60)	
No prior thalidomide only	8 (100)		7 (87.5)	0.12
Prior thalidomide only	5 (71.43)		4 (57.1)	
No prior SCT	13 (92.9)	0.2	11 (78.6)	0.6
Prior SCT	0		0	

* Median number of treatment cycles = 10.25. SCT, stem cell transplantation

Stem cell harvest and transplantation

The two patients who underwent stem cell transplantation received lenalidomide plus low-dose dexamethasone for seven and 10 cycles, respectively. Both patients could successfully collect stem cell with high-dose cyclophosphamide and 10 microgram/kilogram of G-CSF. The first patient, a 64-year-old male, achieved a complete response at the sixth cycle and stem cells were harvested successfully after one procedure; his total CD34+ cell count was 4.3×10^6 cells/kg following 2 days of stem cell collection. The patient received melphalan 200 mg/m^2 as a conditioning regimen for 1 day, and their response was re-evaluated 3 months after stem cell transplantation. This patient achieved a complete response

1 month after the transplantation. The second patient, a 36-year-old female, received two stem cell harvesting procedures because her initial overall CD34+ cell count was 1.5×10^6 cells/kg following 3 consecutive days of stem cell collection. She then received melphalan 200 mg/m^2 as a conditioning regimen and was admitted for autologous stem cell transplantation. This patient also achieved a complete response, 3 months after stem cell transplantation.

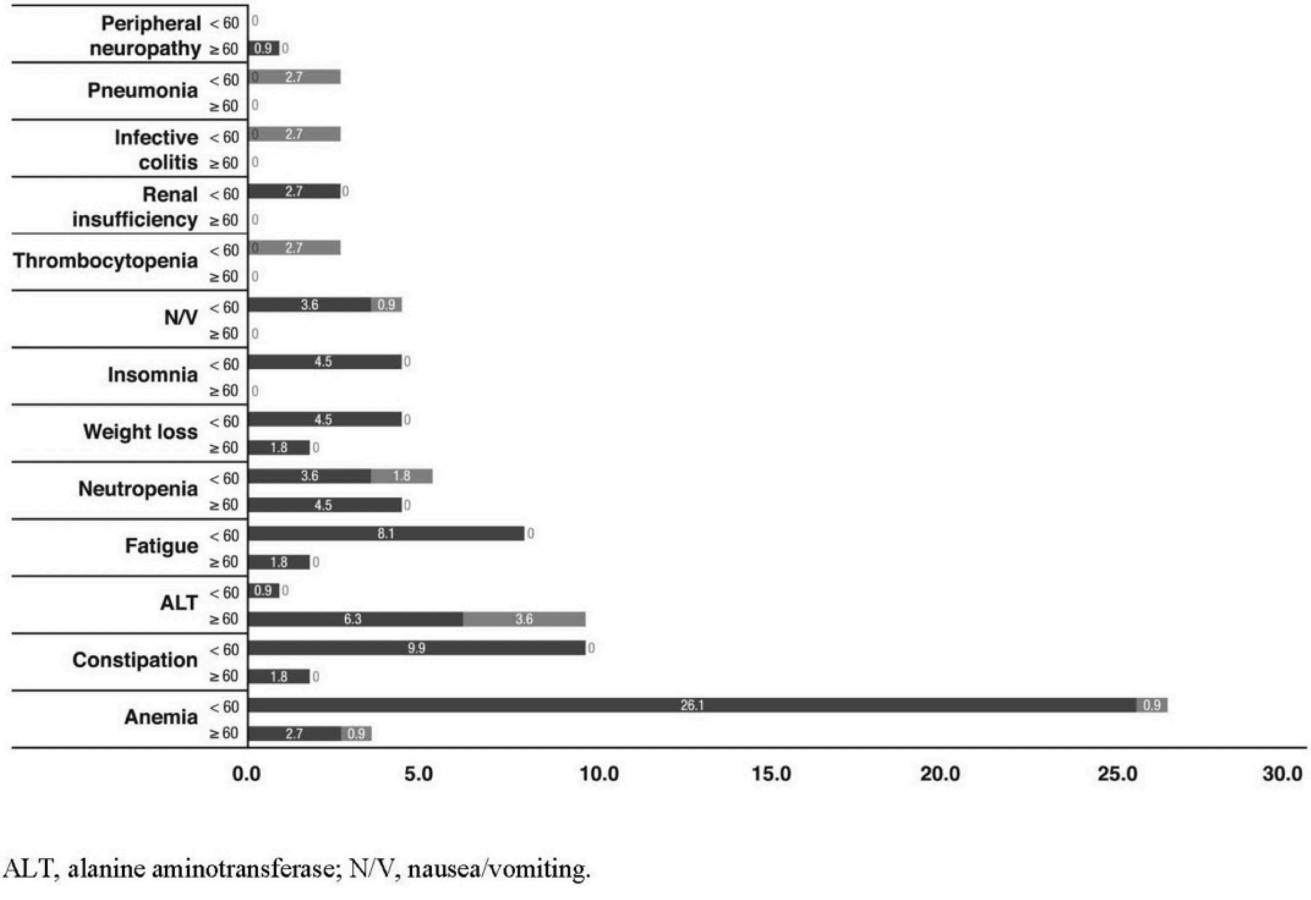
Treatment toxicity

The most common treatment-related toxicities were hematologic events. Overall, 50% of patients had at least one episode of hematologic toxicity, anemia, and/or neutropenia. However, none of the patients reported grade 3 or 4 neutropenia. The most common non-hematologic toxicity was fatigue. There was no thrombosis events. Other adverse events in patients aged <60 and ≥60 years old are shown in Fig 2. The distribution of adverse events was similar in both age groups, with notable differences shown in the frequency of grade 1-2 anemia, elevated ALT, and constipation between the two groups (2.7%, 6.3%, and 1.8% versus 26.1%, 0.9%, and 9.9%, respectively; Fig 2). The overall frequency and grade of toxicities across the 105 cycles of treatment administered are shown in Fig 3.

One patient who achieved a stringent complete response after eight cycles reported progressive disease with meningeal involvement following the twelfth treatment cycle.

DISCUSSION

Lenalidomide plus dexamethasone has demonstrated clinical efficacy in both relapsed/refractory multiple myeloma and newly diagnosed myeloma.[5-8] This is the first study to evaluate the use of lenalidomide plus low-dose dexamethasone in relapsed/refractory multiple myeloma patients in Thailand. The ORR reported here (86.7%) is consistent with those reported in prior multinational phase II and phase III trials (MM-009, MM-010) using this regimen.[5,6] Despite failing prior therapy with novel agents such as bortezomib and/or thalidomide, these patients demonstrated a positive response to lenalidomide plus low-dose dexamethasone.



ALT, alanine aminotransferase; N/V, nausea/vomiting.

Fig 2. Frequency and grade of adverse events/toxicities by age group.

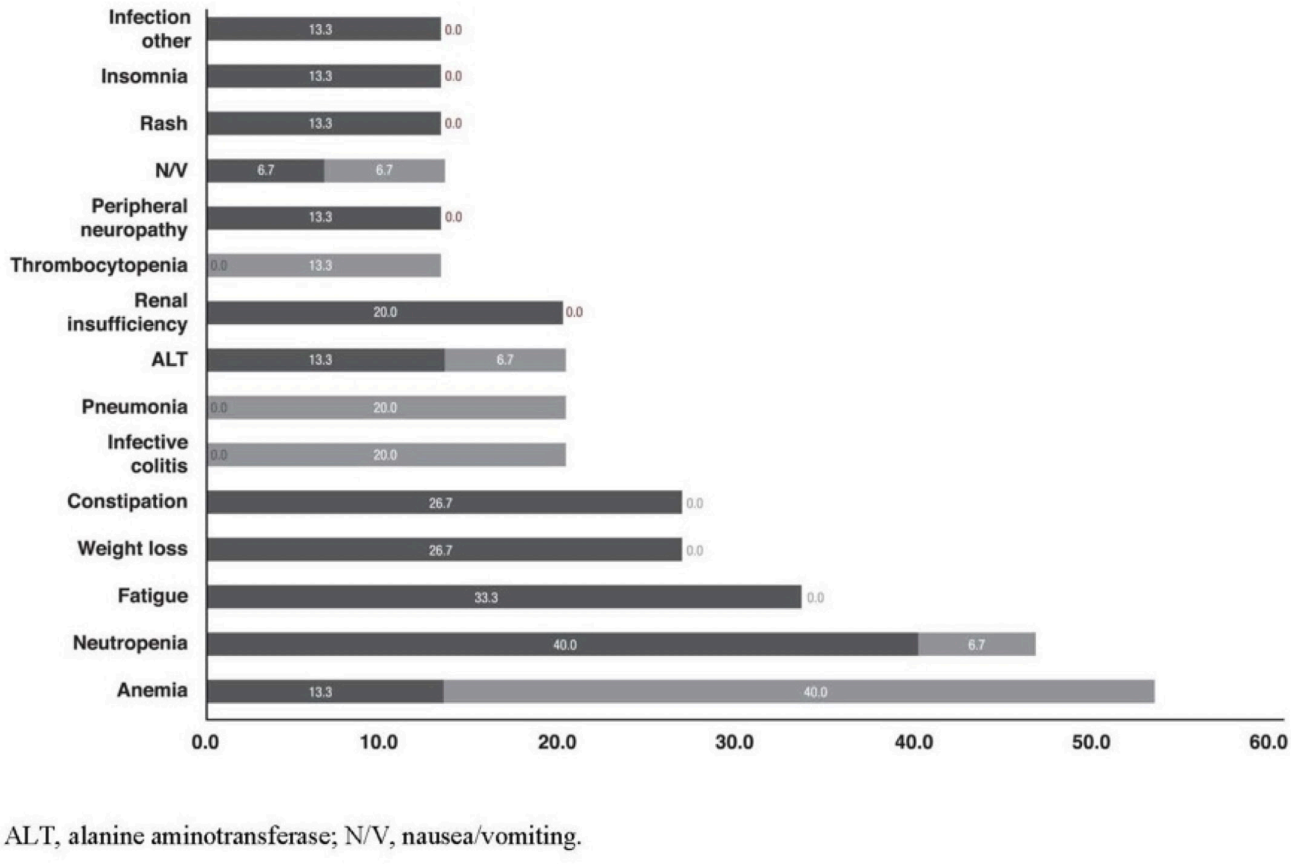


Fig 3. Frequency and grade of adverse events/toxicities across all treatment cycles.

There are few studies in the English literature investigating the efficacy of novel regimens in treatment-refractory multiple myeloma in Asia, with even fewer studies investigating lenalidomide in these patients. At our hospital in Thailand, patients with newly diagnosed multiple myeloma typically receive immunomodulatory (IMiD)- or bortezomib-based regimens, or a combination of both; if patients achieve a complete response, they then receive approval for stem cell transplantation. For patients with relapsed/refractory disease, the initial treatment regimen may be switched; if patients are candidates for transplantation, melphalan-based combinations are not used. The majority of patients receive bortezomib or IMiDs with cyclophosphamide-based conventional chemotherapy, such as VAD or DCEP. The introduction of lenalidomide further increases the treatment choice for multiple myeloma, warranting its evaluation for safety and efficacy in Thai patients.

Bortezomib- and thalidomide-based salvage therapies have demonstrated efficacy in Korean patients, with ORR of 88% - 90% reported in one clinical study.[14] Similarly high response rates (100%) were observed in an open-label study of Japanese patients with relapsed/refractory multiple myeloma receiving a combination of lenalidomide plus dexamethasone.[15] A retrospective study investigating the use of thalidomide plus high-dose dexamethasone in Thailand in newly diagnosed and treatment-refractory multiple myeloma patients reported an ORR of 92%, which is similar only to that reported in our study of treatment-refractory multiple myeloma patients.[16] The high response rates reported here support the available data in the literature and confirm the efficacy of lenalidomide in treating refractory multiple myeloma in an Asian population. However, heavily pretreated patients showed lower response when compared with patients who received ≤2 lines. In addition, the only patient who exposed to transplantation did not response well with this regimen.

Hematologic toxicities were the most common treatment-related adverse events reported in this study. However, in contrast to those reported in other studies, the most frequently reported toxicity was anemia rather than neutropenia.[5-8,16,17] Both anemia and neutropenia were manageable using transfusion and dose-reduction strategies.

The median dose of lenalidomide in patients aged >60 years old was 15 mg/day. Patients received dose reductions from the initial 25 mg/day primarily because of fatigue, anemia, and neutropenia. Following lenalidomide-dose adjustment, the toxicity profile improved in patients

aged ≥60 years old, although most of these patients reported disease progression after responding to therapy at the fourth treatment cycle. Renal impairment was another important factor leading to dose reduction. One such patient developed grade 2 neutropenia, which was successfully managed with dose reduction and appropriate correction for the renal impairment.

Our study is limited by its open-label, single-arm design, and the small size of the patient population. While the focus of our study was on treatment response, analyses incorporating progression-free and overall survival may have provided further insights into the efficacy of lenalidomide in treatment-experienced patients. Despite these limitations, the findings support the use of lenalidomide in treatment-refractory multiple myeloma, particularly in an Asian population. Our findings are consistent with data from multinational studies and also those of other Asian studies.[5,6,14-16] A larger scale, long-term randomized clinical trial would further confirm the safety and efficacy of lenalidomide for multiple myeloma in Thai patients.

Novel agents can significantly improve progression-free survival and overall survival in multiple myeloma patients. However, health insurance in Thailand does not cover the use of lenalidomide, except government health coverage. Our study showed excellent outcomes in this group of patients. In addition, this regimen is an outpatient-based regimen. Therefore, a socioeconomic study is important for the further adaptation of this regimen into all health coverage for patients' benefit.

In conclusion, the regimen of lenalidomide and low-dose dexamethasone was found to be highly effective in Thai patients with relapsed and/or refractory multiple myeloma; adverse events were manageable with an acceptable toxicity profile. Our findings suggest that lenalidomide 15 mg/day is a safe and effective dose for Thai patients older than 60 years old. This combination could be a new standard treatment in relapsed/refractory multiple myeloma in Thailand.

ACKNOWLEDGMENTS

We are grateful to all participating patients and our clinical and laboratory colleagues for their collaboration and support throughout this trial. The study was supported by the Thai Society of Hematology and the Faculty of Medicine of Siriraj Hospital, Bangkok. Lenalidomide for use in this study was donated by Celgene Corporation. Medical editorial assistance was provided by Timothy Stentiford of MediTech Media Asia. Medical editorial assistance was supported by Celgene Corporation.

Conflicts of interest: There are no conflicts of interest to declare.

REFERENCES

1. Kunacheewa C, Orlowski RZ. New Drugs in Multiple Myeloma. Annu Rev Med 2019;70:521-47.
2. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. New Engl J Med 2014;372:142-52.
3. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. New Engl J Med 2015;373:621-31.
4. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. New Engl J Med 2016;375:1319-31.
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. New 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. New 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. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37.
9. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115-23.
10. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.
11. Dimopoulos MA, Palumbo A, Attal M, Beksac M, Davies FE, Delforge M, et al. Optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement. Leukemia 2011;25:749-60.
12. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-23.
13. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.
14. Ahn JS, Yang DH, Jung SH, Park HC, Moon JH, Sohn SK, et al. A comparison of bortezomib, cyclophosphamide, and dexamethasone (Vel-CD) chemotherapy without and with

thalidomide (Vel-CTD) for the treatment of relapsed or refractory multiple myeloma. Ann Hematol 2012;91:1023-30.

15. Iida S, Chou T, Okamoto S, Nagai H, Hatake K, Murakami H, et al. Lenalidomide plus dexamethasone treatment in Japanese patients with relapsed/refractory multiple myeloma. Int J Hematol 2010;92:118-26.

16. Niparuck P, Sorakhunpipitkul L, Atichartakarn V, Chuncharunee S, Ungkanont A, Aungchaisuksiri P, et al. Treatment outcome of thalidomide based regimens in newly diagnosed and relapsed/refractory non-transplant multiple myeloma patients: a single center experience from Thailand. J Hematol Oncol 2010;3:1.

17. Dimopoulos MA, Hussein M, Swern AS, Weber D. Impact of lenalidomide dose on progression-free survival in patients with relapsed or refractory multiple myeloma. Leukemia 2011;25:1620-6.