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Limited benefits of thalidomide and dexamethasone maintenance after autologous stem cell transplantation in newly diagnosed multiple myeloma patients: a prospective phase II multi-center study in Korea

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ABSTRACT

Although the clinical outcome of newly diagnosed multiple myeloma has improved with maintenance therapy, maintenance with novel agents is not always available depending on medical expenses or drug accessibility. We intended to investigate the efficacy and toxicity of thalidomide/dexamethasone maintenance in Korean patients. In this multicenter phase 2 study, patients with newly diagnosed myeloma who underwent induction chemotherapy followed by autologous stem cell transplantation (ASCT) were enrolled

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to receive maintenance treatment of 100mg thalidomide daily for 28 days and 40mg dexamethasone daily for 4 days each cycle. Maintenance was given up to 12 cycles. The primary endpoint was a 1-year event free survival (EFS) rate. It was assumed that EFS at 1-year would be 91% with thalidomide and 1-year EFS below 82% would be of no effect. A total of 43 patients were consecutively enrolled (median age, 58 years [range, 34 – 65]; male, $n = 31$). With a median follow-up duration of 17.3 months (range, 1.1 – 32.2), EFS at 1 year was 65.1% (95% confidence interval [CI], 48.9 – 77.3). PFS and OS at 1 year was 85.6% (95% CI, 70.7 – 93.3) and 90.4 (95% CI, 76.3 – 96.3), respectively. In terms of side effects, 39 patients (90.7%) experienced adverse events (AEs) of any grade, and 14 patients (32.6%) experienced grade 3 or 4 adverse events. 15 patients (34.9%) failed to complete 12 cycles of maintenance, and the most common reason for premature termination was AEs ($n = 6$). In Korean patients the benefits of thalidomide maintenance does not seem to outweigh the toxicity of thalidomide, especially in high-risk MM. Considering the long clinical course of MM, preservation of quality of life and finances might be more beneficial for subsequent MM treatment.

ARTICLE INFO

Keywords: Multiple myeloma; Maintenance; Thalidomide; Autologous stem cell transplantation

Introduction

Multiple myeloma (MM) has long been heralded as an incurable cancer. However, with introduction of proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and monoclonal antibodies and now chimeric antigen receptor (CAR) T cell therapy as salvage, the median survival of MM patients has reached 8 to 10 years. [1] Unfortunately, such wide variety of treatment options also means that MM is incurring more and more medical cost per person. As such, the success and longevity of the first line treatment remains the key to better outcomes and quality of life.

Induction chemotherapy followed by autologous stem cell transplantation (ASCT) and maintenance treatment is considered the standard for newly diagnosed MM. [2,3] For durable progression free survival (PFS), induction therapy with triplet is recommended and quadruple option is being investigated. [3] In the arena of maintenance treatment, thalidomide was first investigated. [4-6] IFM 99-02 study, 1 of the earliest thalidomide trials, reported 36% of 4-year event free survival (EFS) rate and 87% of 4-year overall survival (OS) rate. [4] The subsequent studies failed to show unanimous benefits, [5-7] with varying degree of toxicity. Lenalidomide, on the other hand, showed clear efficacy in terms of EFS and PFS. [8-10] After 2 separate trial results reporting PFS prolongation by almost 20 months with lenalidomide maintenance in 2012, lenalidomide is currently being used in the United States and Europe. More specifically, McCarthy et al. reported that the median PFS was 46 months in the lenalidomide group compared to 27 months in placebo group ($P < 0.001$),[8] while Attal et al. reported that lenalidomide maintenance improved both median PFS (41 months vs 23 months with placebo; hazard ratio 0.5; $P < 0.001$) and EFS (40 months vs 23 months with placebo; $P < 0.001$).[9]

As aforementioned, MM generates substantial economic and social burdens thus the treatment is highly dependent on health-care resource distribution. Due to the cost of lenalidomide, thalidomide is still considered an alternative maintenance treatment option in certain circumstances, and Korea is not an exception. In 2016, retrospective analysis of Korean MM patients showed 55.4% of 3-year PFS rate with 88.0% of 3-year OS rate. [11] Based on this, we prospectively investigated the efficacy and tolerability of thalidomide-based maintenance treatment for newly diagnosed Korean MM patients.

Methods

Patients

This study was a multicenter, single-arm, open-label phase II study conducted at 6 centers in South Korea. From July 2013 to November 2015, newly diagnosed and ASCT eligible patients, defined as those under the age of 65 years according to the national insurance coverage restrictions, were screened for eligibility. There was no restriction with regards to induction chemotherapy, but those achieving partial response (PR) or better with ASCT were finally enrolled. The sample size was estimated according to Dorey's method for effective sample size calculation. [12] It was assumed that EFS at 1-year would be 91% with thalidomide based on previous reports.[6,13-14] A margin of error of plus or minus 9% points at the 95% confidence level was set, therefore calculation reaching 82% of 1-year EFS as the minimal threshold. 1-year EFS below 82% would be of no effect. To have a power of 95% with a two-sided alpha level of 5%, a total of 39 patients was necessary.

Exclusion criteria included European Cooperative Oncology Group (ECOG) performance status score 3 – 4, hepatic impairment (transaminase >2 times of upper normal limit), renal impairment (creatinine clearance <10 ml/min), previous or concurrent malignancies, uncontrolled infection, and active thromboembolism or preexisting peripheral neuropathy. Patients with incomplete hematologic recovery after ASCT (i.e. absolute neutrophil count $< 1.0 \times 10^9$/L, platelet count $<50 \times 10^9$/L, and hemoglobin < 8.0 g/dL) were also excluded.

The protocol was approved by the institutional ethics committee of each participating medical center and the study was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Good Clinical Practice. All participants provided written informed consent prior to the participation in this study.

Study drug schedule, response and adverse events monitoring

Thalidomide was given at a dose of 100mg daily from day 1 to day 28 of each cycle. For each cycle, 40mg of dexamethasone was concurrently administered from day 1 to 4. Dose modifications and interruptions were pre-specified for treatment-related adverse events (AEs). Treatment was planned for a total of 12 cycles but discontinuation was allowed in case of disease progression or unacceptable toxicity. Thrombosis prophylaxis with aspirin or low-molecular weight heparin was recommended from thalidomide initiation to 4 weeks after the last administration of thalidomide.

The treatment response was evaluated according to the International myeloma Working Group response criteria. [15] After the study completion, follow-up data were collected every 2 months until disease progression or 1 year, and then every 3 months thereafter. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. The cytogenetic risk was examined by conventional cytogenetics or fluorescence in situ hybridization (FISH) and categorized as standard and high risk according to IMWG (International Myeloma Working Group) risk stratification. [16]

Study endpoints and statistical analysis

The primary endpoint was EFS at 1 year, and secondary endpoints included PFS and OS. EFS was defined as the time from the date of randomization to the time disease progression, study termination due to serious AEs, or death of any cause. PFS was defined as the time from the date of randomization to the time of progression or death of any cause. OS was defined as the time from the date of randomization to the time of death of any cause. If patients survived without event, the survival was censored at the latest date of follow-up. Data available up to 31 October 2016 were used. The survival curves were estimated using the Kaplan-Meier method.

Categorical data were expressed as percentages and compared using Fisher's exact tests. Continuous data were expressed as medians and compared using Mann-Whitney *U*-test. All analyses

Table 1
Baseline Characteristics.

Characteristic	*n* (%)
Total number of patients	43
Age, years, median (range)	58 (34 – 65)
Male sex	31 (72.1)
ECOG performance status 0/1	14 (32.6)/29 (67.4)
IgG/A/D/light chain disease	32 (74.4)/ 4 (9.3)/ 1 (2.3)/ 6 (14.0)
Cytogenetic risk	
High (del 17p or t(4;14) or t(14;16)	12 (30.0)
Not assessed	3 (7.0)
R-ISS I/II/III	6 (14.0)/ 31 (72.1)/ 6 (14.0)
Induction chemotherapy	
Thalidomide exposure	33 (76.7)
Bortezomib exposure	12 (27.9)
Time from diagnosis to ASCT, months, median (range)	6.3 (3.3 – 34.4)
Time from ASCT to maintenance, months, median (range)	2.6 (1.1 – 4.1)
Conditioning regimen	
High dose melphalan	40 (93.0)
Busulfan + melphalan	3 (7.0)

ECOG: Eastern cooperative oncology group; R-ISS: Revised international staging system; ASCT: Autologous stem cell transplantation.

were conducted based on the intention-to-treat population and thus included all 43 patients. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 43 patients were enrolled at the end. As shown in (Table 1), the median age for all patients was 58 years (range, 34 – 65 years) and 16 patients (37.2%) were over 60 years old. Among 43 patients, 6 patients (14.0%) had revised international staging system (R-ISS) III disease and 12 patients (27.9%) had high-risk MM. The median time from diagnosis to ASCT was 6.3 months, and the median time from ASCT to maintenance start was 2.6 months.

Most of the patients (93.0%) used high dose melphalan conditioning. After ASCT, 22 patients (51.2%) achieved complete response (CR) or stringent CR (sCR), 8 patients (18.6%) achieved very good partial response (VGPR), and 13 patients (30.2%) achieved PR (Table 2). The 5 patients who showed less than PR to induction chemotherapy achieved sCR (1 patient), CR (2 patients) and VGPR (2 patients) with ASCT.

Efficacy of thalidomide maintenance

Median follow-up duration was 19.9 months (range, 3.9 – 35.0 months) from ASCT and 17.3 months (range, 1.1 – 32.2 months) from randomization. During maintenance, 29 patients remained CR, 6 showed VGPR, and 4 showed PR. With thalidomide maintenance, 10 patients (23.3%) showed improved response: 3 patients with PR after ASCT and 4 patients with VGPR after ASCT achieved CR with thalidomide maintenance. The number of the patients at each cycle and serial response during maintenance treatment are presented in (Fig 1).

Among the patients with high-risk MM, the best response of the maintenance treatment was CR in 9 patients (75.0%), VGPR in 1 patient (8.3%), PR in 1 patient (8.3%) (Table 2). 1 patient showed progression only after 2 cycles of treatment. In this group of patients, 2 patients in 12 patients (16.7%) showed improved response with thalidomide maintenance: 1 patient from PR after ASCT to VGPR with thalidomide maintenance, and another patient from PR to CR.

Table 2
Best treatment response at each treatment phase.

Response	Induction		ASCT		Maintenance	
All patients (n = 43)						
sCR	0	(0.0)	10	(23.3)	11	(25.6)
CR	4	(9.3)	12	(27.9)	18	(41.9)
VGPR	12	(27.9)	8	(18.6)	6	(14.0)
PR	22	(51.2)	13	(30.2)	4	(9.3)
<PR	5	(4.7)		0	4	(9.3)
Patients with high-risk† multiple myeloma (n = 12)						
sCR	0	(0.0)	5	(41.7)	4	(33.3)
CR	2	(16.7)	3	(25.0)	5	(41.7)
VGPR	2	(16.7)	1	(8.3)	1	(8.3)
PR	6	(50.0)	3	(25.0)	1	(8.3)
<PR	2	(16.7)		0	1	(8.3)

†High-risk is defined as 17p deletion or t(4;14) or t(14;16).
ASCT: Autologous stem cell transplantation; sCR: Stringent complete remission; CR: Complete remission; VGPR: Very good partial response; PR: Partial response.

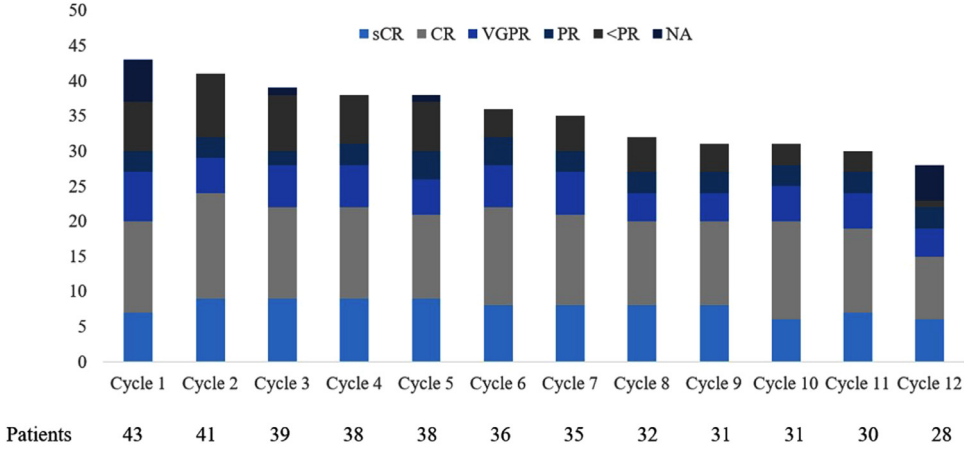

Fig. 1. The number of patients at each maintenance treatment cycle and the treatment response.

At the time of data cutoff, 21 events occurred. Primary outcome of 1-year EFS was 65.1% (95% confidence interval [CI], 48.9 – 77.3%) and 2-year EFS rate was 46.7% (95% CI, 29.0 – 62.6%). PFS was 85.6% (95% CI, 70.7 – 93.3%) at 1 year and 62.5% (95% CI, 41.9 – 77.6%) at 2 year. OS at 1 year and 2 year were 90.4% (95% CI, 76.3 – 96.3%) and 85.6% (95% CI, 67.3 – 94.1%), respectively (Fig. 2).

Study drug adherence

Overall, 65.1% of patients (n = 28) completed preplanned twelve cycles of thalidomide and dexamethasone maintenance. The median treatment duration of entire patients was 11.4 months (range, 0.6 – 12.8 months). Among 15 patients (34.9%) who failed to complete twelve cycles of maintenance, the median time to discontinuation was 5.6 months (range, 0.6 – 11.6 months). The most common reason for premature termination was AEs (n = 6), followed by disease progression (n = 4) and withdrawal of informed consent (n = 3). Mean dose intensity was 41.1% (range, 8.3 – 91.7 of total planned dose) among the patients who experienced early termination whereas the mean dose-intensity of thalidomide was 81.1% (range, 33.3% – 100.0%) among

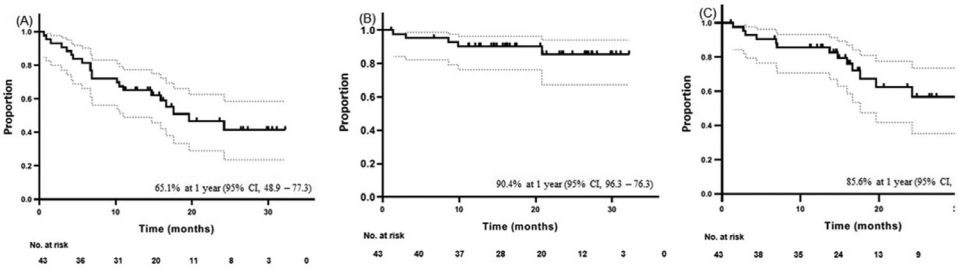

Fig. 2. Survival curves.
(A) Event free survival (EFS), EFS at 1 year was 65.1% (95% CI, 48.9 – 77.3%)
(A) Overall survival (OS), OS rate at 1 year was 90.4% (95% CI, 76.3 – 96.3%)
(B) Progression free survival (PFS), PFS rate at 1 year was 85.6% (95% CI, 70.7 – 93.3%).

Table 3
Dose and Schedule Modification During Trial.

Cycle	Dose reduction	Schedule delay	Study termination
	(n = 31)	(n = 12)	(n = 15)
1	5 Adverse event (3) Investigator's decision (2)	0	2 Adverse event (pneumonia) (1) Treatment refusal (1)
2	10 Adverse event (6) Investigator's decision (4)	3 Adverse event (2) Investigator's decision (1)	2 Adverse event (2) (Fulminant hepatitis, infection)
3	8 Adverse event (5) Investigator's decision (3)	2 Adverse event (1) Others (dental check) (1)	1 Disease progression (1)
4	5 Adverse event (4) Investigator's decision (1)	1 Adverse event (1)	
5	3 Investigator's decision (3)	1 Adverse event (1)	2 Disease progression (1) Investigator's decision (1)
6	5 Adverse event (2) Investigator's decision (3)	2 Adverse event (1) Others (patient schedule) (1)	1 Adverse event (DVT) (1)
7	0	0	3 Adverse event (neuropathy) (1) Disease progression (1) Treatment refusal (1)
8	1 Adverse event (1)	2 Adverse event (1) Others (patient schedule) (1)	1 Disease progression (1)
9	3 Adverse event (1) Investigator's decision (2)	2 Adverse event (2)	
10	2 Adverse event (2)	5 Adverse event (5)	
11	1 Adverse event (1)	0	1 Adverse event (neuropathy) (1)
12	1 Investigator's decision (1)	4 Adverse event (3) Others (patient schedule) (1)	2 Treatment refusal (1) Investigator's decision (1)

the patients who completed the study. Eighteen patients (41.9%) experienced thalidomide dose modification and 12 patients (27.9%) experienced schedule delay at least once during the trial, both of which were mainly due to AEs. Detailed information on dose and schedule modification is presented in (Table 3).

Safety of thalidomide maintenance

As shown in (Table 4), any AEs related to treatment occurred in 90.7% of the patients and AEs graded more than 3 occurred in 14 patients (32.6%). The most common AE was peripheral neuropathy (PN). During the total study period, 41.9% (n = 18) of patients experienced PN of any

Table 4
Adverse Events.

Toxicities	Any		≥Grade 3	
General				
General weakness	3	(7.0)	2	(4.7)
Fatigue	3	(7.0)	1	(2.3)
Weight gain	3	(7.0)	0	(0.0)
Gastrointestinal				
Constipation	7	(16.3)	0	(0.0)
Hepatitis	2	(4.7)	1	(2.3)
Hematologic				
Neutropenia	5	(11.6)	5	(11.6)
Infectious				
Upper respiratory infection	12	(27.9)	0	(0.0)
Pneumonia	2	(4.7)	2	(4.7)
Others	3	(7.0)	1	(2.3)
Neurologic				
Peripheral sensory neuropathy	18	(41.9)	2	(4.7)
Dizziness	3	(7.0)	0	(0.0)
Endocrine				
Hyperglycemia	3	(7.0)	0	(0.0)
Musculoskeletal				
Arthralgia	5	(11.6)	0	(0.0)
Facial edema	3	(7.0)	0	(0.0)
Dermatologic				
Skin rash	6	(14.0)	0	(0.0)
Pruritus	4	(9.3)	0	(0.0)
Miscellaneous				
Hiccup	2	(4.7)	1	(2.3)

grade. Two patients experienced PN of grade 3 or higher. With thalidomide dose modification, 16/18 patients reported decrease in the pain severity, but 2 patients ended up discontinuing the treatment due to PN. The mean dose intensity of thalidomide in these patients was 68.2% (range, 22.9% – 100.0%) and mean time elapsed between randomization and the onset of the AE was 3.9 months (range, 0.5 – 9.6 months).

Any grade AEs related to hematologic toxicity occurred in 6 patients (5 neutropenia, 1 anemia). Unlike the neurologic symptom, all neutropenia cases were grade 3 or 4. Infection occurred in 19 patients (44.2%). The majority of the infection was an upper respiratory infection and manageable, but 1 patient with pneumonia and 1 patient with fulminant hepatitis died during the study. Aspirin was administered to 42 patients for thrombosis prophylaxis. Venous thromboembolism (VTE) occurred in 1 patient.

Discussion

This is a multicenter phase II trial to investigate the feasibility and tolerability of thalidomide maintenance treatment following ASCT in Korean patients. In this study, we included patients who had been exposed to thalidomide or bortezomib prior to maintenance and used 100mg of thalidomide for 1 year. As a result, 1-year EFS was 65.1% and 2-year PFS and OS were 62.5% and 85.6%, respectively. Compared with previous studies on thalidomide maintenance, our study also showed comparable survival outcomes. However, since the initial hypothesis was that 1-year EFS below 82% would be of no effect, this study failed to prove definitive benefits of thalidomide maintenance. Also, even with a relatively low dose of thalidomide (100mg) compared with other randomized trials and limited maintenance duration of 12 months, AEs occurred quite frequently and 6 patients (14%) discontinued maintenance earlier than planned schedule due to AEs.

PN was the most frequently encountered AE, and occurred in 41.9% of patients ($n = 18$) throughout the whole study period. Although severe PN (≥ grade 3) was not frequent owing to dose adjustment per protocol, it was still a major cause of treatment cessation and sched-

ule delay. Previous studies were designed either to administer a high dose of thalidomide or to continue thalidomide indefinitely until progression. [4,6,7] As a result, after 1 year of treatment, more than 30% of the study population was not able to tolerate the treatment majorly due to AEs. [5,17] Even with only 100mg of thalidomide in this study, the incidence of AE was still high and mean dose intensity among the patients with PN were only 67.2% (range, 8.3% – 100%) of planned dose. Compromised quality of life is often overlooked but an important aspect of treatment, and without definitive benefits high rates of drug intolerance do not favor the use of the drug.

Due to its low hematotoxicity profile and oral availability, thalidomide became the logical candidate for maintenance therapy choice in the late 2000′s. A significant improvement in EFS and OS was initially seen in the Intergroupe Francophone du Myelome 99 02 study,[4] but after long-term follow-up of patients with cytogenetics available, the previously observed survival benefit was not maintained with an estimated 5-year OS rate of 74%. Patients with high-risk MM especially showed propensity towards poor prognosis with thalidomide maintenance, as in previous reports. In MRC IX, patients with adverse cytogenetic abnormalities were unlikely to benefit from thalidomide maintenance. [7] Specifically, patients with adverse cytogenetic abnormalities showed similar PFS (9 vs 12 months; $P = 0.48$) but worse OS ($P = 0.009$) with thalidomide maintenance. Considering the fact that 30% of our study population constituted high-risk MM, it is not surprising that we observed lower-than-expected benefits with thalidomide maintenance. Likewise, other studies comparing thalidomide to other novel agents in the induction setting also showed that thalidomide could not overcome the effect of adverse cytogenetic abnormalities. [18,19] Since more recently developed drugs including lenalidomide showed benefits even in high-risk MM, [20] these patients should be subjected to maintenance with more potent IMiDs, and not thalidomide.[21]

Although lenalidomide is widely used as maintenance, due to government regulation and reimbursement issues post-transplant lenalidomide is still not available in many countries. As such the cost-effectiveness and survival benefit of thalidomide maintenance is continuously being investigated. [22,23] Australian group reported updated survival data of ALLG MM6 trial, [22] and the investigators concluded that thalidomide maintenance can be an effective strategy considering life-year saved by thalidomide and many other social and clinical factors that might affect medical expenses, especially when lenalidomide is not available. The long-term follow-up results of Total Therapy 2 and HOVON-50, which adopted thalidomide from the start of the induction phase, also reported benefits in OS with more than 5 years of long-term follow-up. [23,24] However, since these studies mainly included Caucasian patients and used higher dose of thalidomide, these results cannot be readily extrapolated to Asian patients who are more fragile.

1 of the most obvious pitfall of this study is the small number of patients with heterogeneous disease characteristics. Also, cost-effectiveness analyses would have solidified our results, but due to relatively short follow-up duration it was not possible. However, since our findings provide further understandings for physicians to infer decision-making nuances regarding appropriate and realistic MM treatment sequence, we believe our study deserves academic attention.

Conclusions

In conclusion, in Korean patients the benefits of thalidomide maintenance does not seem to outweigh the toxicity of thalidomide, especially in high-risk MM. The use of thalidomide maintenance should be restricted to fit patients without high-risk MM and evidence of PN. Considering the long clinical course of MM, preservation of quality of life and finances might be more beneficial for subsequent MM treatment.

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