의학석사 학위논문

Thalidomide and dexamethasone maintenance after autologous stem cell transplantation in newly diagnosed multiple myeloma patients: A prospective multicenter study in Korea

새롭게 진단된 다발골수종 환자에서
자가조혈모세포이식 후 탈리도마이드와
덱사메타손 유지요법에 대한 전향적 다기관 연구

2019년 2월

서울대학교 대학원
의학과 중개의학
김 상 아

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지도교수 윤 성 수

이 논문을 의학석사 학위논문으로 제출함

2018년 10월

서울대학교 대학원

의학과 중개의학

김 상 아

김상아의 석사 학위논문을 인준함

2019년 1월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

Abstract

Thalidomide and dexamethasone maintenance after autologous stem cell transplantation in newly diagnosed multiple myeloma patients: A prospective multicenter study in Korea

Sang-A Kim
Graduate School of Translational Medicine
Seoul National University College of Medicine

Clinical outcome of multiple myeloma has been improved with maintenance therapy. Thalidomide is the first immunomodulatory drug to be studied as maintenance therapy and has widely been used in Korea in spite of the concerns about uncertain survival benefit and considerable side effects. Currently, next-generation immunomodulatory drugs and proteasome inhibitors are actively investigated as promising maintenance treatment. However, in real clinical practice, it is often difficult to use these new drugs because of medical expense or drug accessibility. In such a situation, thalidomide is still considered to be an applicable alternative.

From this point of view, this study is an open-label, multicenter, prospective phase II study to investigate the efficacy and toxicity of thalidomide maintenance in Korean patients who were newly diagnosed with multiple myeloma.

Patients who underwent induction treatment followed by autologous stem cell transplantation were enrolled in this study. Treatment was planned for a total of 12 cycles, but terminated in case of disease progression or unacceptable toxicity. Each cycle was scheduled for 28 days, with 28 days of thalidomide at a dose of 100 mg and 4 days of dexamethasone at a dose of 40 mg. The primary endpoint of this study was event-free survival (EFS) at 1 year, which was defined as the time from randomization to disease relapse, progression, serious side effects or death of any cause. Key secondary endpoints included progression free survival (PFS), overall survival (OS) and toxicity profile.

From July 2013 to November 2015, a total of 43 patients from 7 medical centers were consecutively enrolled. Median follow-up duration of study participants was 17.3 months (range, 1.1 - 32.2 months). Only 28 patients (65.1%) completed all 12 cycles of maintenance treatment, and median duration of treatment was 5.6 months (Interquartile range [IQR], 2.9 - 6.9 months) in patients who experienced early termination of the study.

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, 96.3 - 76.3), respectively. Of those who failed to achieve a complete response after autologous stem cell transplantation, 4 patients with partial

response and 3 patients with very good partial response attained complete response during maintenance treatment. In univariate analysis of EFS, there were no clinical factors that were significantly associated with EFS. However, in univariate analysis for PFS, patients with previous thalidomide exposure benefitted with thalidomide maintenance (Hazard ratio [HR] 0.32; 95% CI, 0.11 - 0.95; p = 0.041). In terms of side effects, 39 patients (90.7%) experienced adverse events of any grade, and 14 patients (32.6%) experienced grade 3 or 4 adverse events. Peripheral neuropathy, which is a well-described side effect of thalidomide, occurred in 20 patients (46.5%) during the total study period. Thalidomide dose was modified in case of peripheral neuropathy, but it was still most common side effect that caused early termination of treatment.

To summarize, thalidomide showed comparable efficacy with previously reported Western studies. But a considerable proportion of patients experienced adverse events which caused treatment cessation. In conclusion, if there is a limitation in maintenance with other novel agents, thalidomide can be a reasonable strategy although side effects draw concern.

Keyword Multiple myeloma, thalidomide, maintenance, autologous stem cell transplantation

Student number: 2017-21290

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Introduction

Multiple myeloma is a neoplasm of plasma cells that presents characteristic symptoms of target organ damage. It accounts only one percent of all cancers but is the second most common hematologic malignancy worldwide, occupying 10% of all hematologic malignancies. The incidence of multiple myeloma varies by region and is generally higher in Western countries (1). Actually, about 30,000 new cases are diagnosed in the United States each year (2). In Korea, the incidence of multiple myeloma has been increasing and has doubled over the past decade (3). This trend suggests that multiple myeloma will emerge as an important hematologic disease in Korea in the near future.

Since the 1960s, when alkylating agents and steroid began to be used to treat myeloma, there has been a steady development of treatment strategy (4). Particularly, in the 2000s, the introduction of novel agents into medical practice markedly improved the prognosis of myeloma patients (5). Proteasome inhibitors and immunomodulatory agents are currently the most widely used novel agents, and the next generation of these drugs are being actively investigated. Furthermore, a wide variety of new drugs are being studied, from histone deacetylase inhibitors to immune checkpoint inhibitors and even chimeric antigen receptor cell therapies. (6). With further understanding of disease and the develop ment of treatment options, median survival of myeloma patients reached 8 to 10 years (7). It is expected that a

variety of drugs investigated would even broaden the therapeutic options and improve clinical outcome (8).

However, even with these accomplishments, myeloma is still far from a curable disease. Most of the myeloma patients experience disease relapse or progression eventually, which is one of the most serious challenges in myeloma treatment. Thus, optimal long-term disease control strategies are as important as potent induction therapy and is actually endorsed in major guidelines (9, 10). In this context, the endeavor to find optimal consolidation or maintenance therapy was made. This means not only an arithmetic prolongation of progression-free and overall survival duration, but also maintaining the quality of life even with the long-lasting treatment. Thus, the drug must be convenient, economical and well-tolerated, needless to say about efficacy.

Thalidomide is an oral immunomodulatory agent that was first to be used in multiple myeloma based on the clinical studies demonstrating its efficacy in multiple myeloma (11). Thalidomide shows its anti-neoplastic effect through anti-angiogenic effect, and they also play important role in T-cell and natural killer cell function modification and cytokine elaboration (12). After showing its efficacy on induction treatment, since the 2000s, thalidomide has been studied from the perspective of maintenance. IFM 99-02 was one of the earliest trials of that reported promising clinical results with thalidomide maintenance, reporting benefits in response rate, event-free survival and overall survival. Also, thalidomide in this trial improved the quality

of response, even in patients who did not have a very good partial response after autologous stem cell transplantation (ASCT) (13). Various study groups conducted randomized-controlled trials on this issue, even though treatment regimens and duration slightly differed from studies to study. These studies commonly revealed that considerable patients experienced, and to some extent, even stopped the maintenance due to toxicity. Major toxicity that hindered the treatment was peripheral neuropathy (PN) and thromboembolism. And most importantly, they showed conflicting results about the potential benefit of thalidomide on overall survival. These problems were major obstacles to using thalidomide in real clinical practice. ~~And~~ Additionally, efficacy on the patients who showed disease progression after thalidomide treatment and poor cytogenetics were still in the area of uncertainty.

With this concern, other novel agents were investigated to find better maintenance option comparing with thalidomide. Lenalidomide, an analogue of thalidomide, was most actively investigated immunomodulatory drug. With better potency and safety profile, lenalidomide overcame the limitations of thalidomide, showing promising results in the maintenance setting (14-16). Recent meta-analysis analyzing major clinical trials on lenalidomide maintenance showed PFS and OS benefit (17). By current major guidelines, it is now widely approved as the mainstay of maintenance therapy (9, 10). But other classes of novel agents including a proteasome inhibitor and monoclonal antibody are still investigated to seek for most effective and patient-tailored

treatment.

Despite these advances, however, there are some cases that we cannot adopt standard treatment in real clinical practice. Because of the limited choice of new drugs due to drug accessibility and health insurance coverage, it is practically difficult to apply all of the preceding frontline therapies to clinical practice. In this perspective, the purpose of this study is to investigate the utility and tolerability of thalidomide maintenance after ASCT in Korean patients to ascertain the efficacy of thalidomide maintenance in patients without other maintenance options.

Methods

Patients

Patients aged 20 years or older with newly diagnosed multiple myeloma were screened for this study. Induction chemotherapy was at the discretion of the attending physician, but a patient had to achieve a partial response (PR) or better if thalidomide was included in the induction regimen. All patients underwent ASCT within 3 months from induction treatment. Patients achieving at least PR after autologous stem cell transplantation and did not have evidence of progressive disease at the time of registration were finally eligible for this study.

Exclusion criteria included European Cooperative Oncology Group (ECOG) performance status score of more than 3, hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase >2 times of upper normal limit), renal impairment (creatinine clearance <10 ml/min), incomplete hematologic recovery after ASCT, previous or concurrent malignancies, uncontrolled infection, and active thromboembolism or preexisting peripheral neuropathy greater than grade 2.

Trial design

This is a multicenter, single-arm, open-label phase II study conducted at six centers in South Korea. 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 on Harmonization Good Clinical Practice. All participants provided written informed consent prior to study enrollment.

Patients received thalidomide at a dose of 100 mg per day from day 1 to day 28 of each 28 day cycle. At each cycle, 40 mg of dexamethasone was concurrently administered from day 1 to day 4. Dose modifications and interruptions were permitted for treatment-related adverse events (AEs). Treatment was planned for a total of 12 cycles but discontinued in case of disease progression or unacceptable toxicity. Thrombosis prophylaxis with aspirin was recommended from the start of the trial to 4 weeks after the last administration.

Disease assessment was performed every 28 days through cycle 12 based on International Myeloma Working Group (IMWG) response criteria (18). After the study completion, follow-up data were collected every 2 months until disease progression, and then 3 months thereafter. Adverse event was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0 among the patients who were

administered thalidomide treatment at least once during the trial. The cytogenetic risk was examined by conventional cytogenetics or fluorescence in situ hybridization (FISH) and categorized as standard and high risk (19).

Study endpoints

The objective of the study was to determine the efficacy and toxicity of thalidomide maintenance in Korean patients. The primary endpoint was 1-year event-free survival (EFS), and secondary endpoints included progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS). The duration of EFS was defined from the date of randomization to the time of relapse, disease progression, and study termination due to serious adverse event or death of any cause. PFS was defined from the date of randomization to the time of progression or death of any cause. Among the patients with complete response (CR), DFS was calculated from the date of randomization to the date of relapse or death of any cause. The safety profile was also investigated.

Statistical analysis

For sample size calculation, we expected 1-year event-free survival would be 91% and 9% of error is allowable. The number of patients to be included was obtained with 90% power and a two-sided alpha level of 5%. Considering 10% of dropout, a total of 43 patients were required.

Categorical data were expressed as percentages and compared using Fisher' s exact tests. Continuous data were expressed as medians and compared using the Mann-Whitney *U*-test. For the time-to-event variables, survival analyses were performed with the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression was used to analyze the effect of risk factors on survival outcome. Multivariable analysis was waived due to low event count per variables (20). All *P*-values are two-sided, and *P*-value less than 0.05 was considered significant. All analyses 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

From July 2013 to November 2015, forty-three patients with newly diagnosed multiple myeloma were consecutively enrolled with data cutoff in October 2016 (Figure 1). All patients received at least one dose of thalidomide and therefore were evaluable for both safety and efficacy. The median age was 58 years (range, 34 - 65) and 16 patients (37.2%) were over 60-years old. Of a total of 43 patients, 18 patients (41.9%) were categorized as international staging system score II or III and 12 patients (30.0%) were categorized as high-risk cytogenetics by conventional cytogenetic study and FISH, which demonstrates high tumor burden or unfavorable tumor biology at diagnosis. At diagnosis, 29 patients (67.4%) presented end organ damage with osteolytic bony lesion most common presentation. The baseline characteristics of the patients are presented in Table 1.

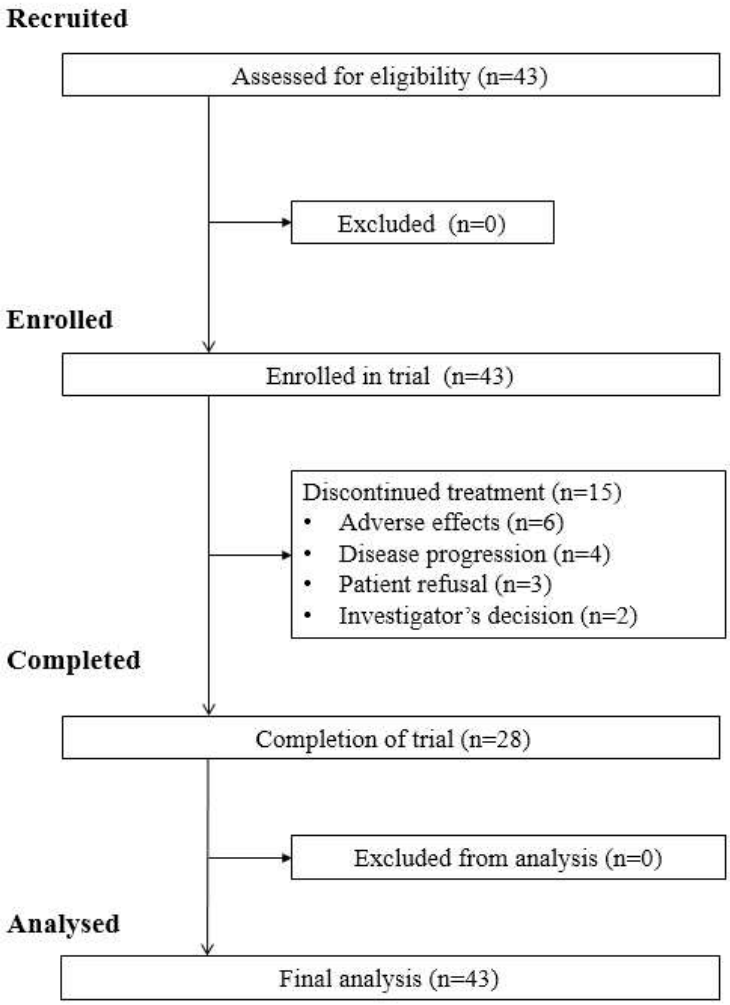

Figure 1. Study flowchart. A total of 43 patients were enrolled in this study, and 15 patients were unable to complete the 12 cycles of preplanned maintenance treatment due to adverse events, disease progression, patients' refusal, or investigators' decision. All 43 patients were included in final efficacy and toxicity analyses as every patient received at least 1 cycle of maintenance treatment.

Table 1. **Baseline patient characteristics (N=43)**

Characteristic	Patients
Age, years, median (range)	58 (34 – 65)
Male sex, n (%)	31 (72.1)
Subtype, n (%)	
IgG, kappa or lambda	32 (74.4)
IgA, kappa or lambda	4 (9.3)
Others†	7 (16.3)
Cytogenetic risk‡,n(%)	
High	12 (30.0)
Standard	28 (70.0)
Not assessed	3 (7.0)
ISS score, n (%)	
I	25 (58.1)
II	10 (23.3)
III	8 (18.6)

B2-macroglobulin at registration, mg/L, median (range)	2.3 (1.3 – 9.9)
Serum albumin at registration, g/dL, median (range)	4.2 (3.5 – 4.9)
Serum creatinine at registration, mg/dL, median (range)	0.9 (0.5 – 7.0)
Induction regimen, n (%)	
Any use of Thalidomide	33 (76.7)
Any use of Bortezomib	12 (27.9)
Time from diagnosis to ASCT, months, median (range)	6.3 (3.3 – 34.4)
Time from ASCT to randomization, months, median (range)	2.6 (1.1 – 4.1)
Conditioning regimen, n (%)	
High-dose melphalan	40 (93.0)
Busulfan-Melphalan	3 (7.0)

†IgD kappa/lambda or light chain disease or non-secretory
‡17p deletion or t(4;14) or t(14;20)
ISS, international staging system; ASCT, autologous stem cell transplantation

Treatment outcome after induction chemotherapy and autologous stem cell transplantation

During induction, 12 patients (27.9%) had received more than single line of treatment. Five patients out of 12 received thalidomide-based treatment, one patient out of 12 received bortezomib-based treatment and the rest received other conventional cytotoxic treatment as their initial treatment. For later line treatment, all patients except for one received bortezomib-based regimen. In total, 33 patients (76.7%) were exposed to thalidomide and 12 patients (27.9%) were exposed to bortezomib during induction therapy. Finally, after induction treatment, 4 patients (9.3%) gained complete response (CR) or stringent complete response (sCR), 12 patients (27.9%) gained very good partial response (VGPR), 22 patients (51.2%) gained partial response (PR), and 5 patients (11.6%) gained stable disease (SD).

ASCT was performed median of 6.3 months (range, 3.3-34.4 months) after the initiation of induction treatment. Most of the patients (93.0%) received high-dose melphalan with autograft. With the completion of ASCT, 22 patients (51.2%) achieved CR or sCR, 8 patients (18.6%) achieved VGPR, and 13 patients (30.2%) achieved PR.

Efficacy of thalidomide maintenance

Median follow-up duration was 19.9 months (range, 3.9-35.0) from ASCT and 17.3 months (range, 1.1-32.2) from randomization. Median time from ASCT to the start of the maintenance was 2.6 months (range, 1.1-4.1 months). During maintenance, the best response of the patients was CR or sCR in 29 patients, VGPR in 6 patients, and PR in 4 patients, with 7 more patients additionally achieved CR including 3 VGPR patients and 4 PR patients. But in contrary, 3 patients with PR and 1 patient with VGPR showed disease progression despite thalidomide maintenance. All but one patient who benefitted from thalidomide did not show poor cytogenetic feature. The response after each treatment phase is summarized in Table 2.

At the time of data cutoff, 21 events occurred. Primary outcome of 1-year probability of event-free survival (EFS) was 65.1% (95% CI, 48.9 - 77.3) and 2-year EFS rate was 46.7% (95% CI, 29.0 - 62.6). Progression-free survival (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. Overall survival (OS) at 1 year and 2 year were 90.4% (95% CI, 96.3 - 76.3) and 85.6% (95% CI, 67.3 - 94.1), respectively. Of patients achieved CR, 2-year disease-free survival was 56.7 % (95% CI, 29.3 - 76.9) (Figure 2).

Table 2. Treatment response at each treatment phase (N=43)

Response category	Induction	ASCT	Maintenance
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 (11.6)		4 (9.3)

ASCT, autologous stem cell transplantation; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response

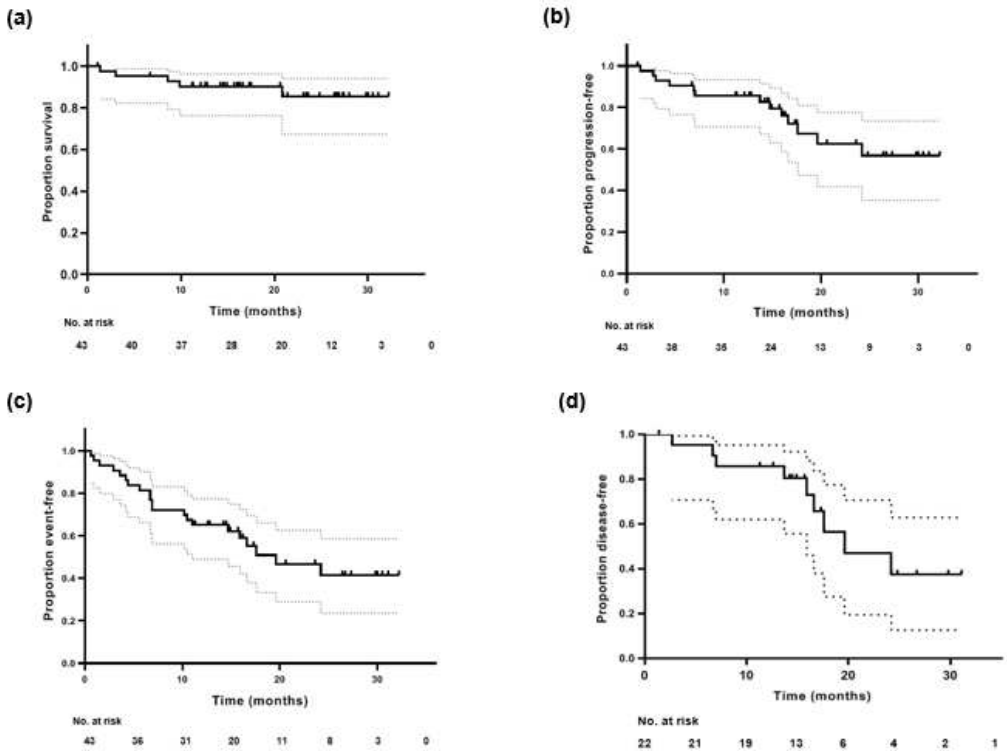

Figure 2. Survival analysis of study population. (a) OS rate at 1 year was 90.4% (95% CI, 96.3 - 76.3) and (b) PFS rate at 1 year was 85.6% (95% CI, 70.7 - 93.3). (c) EFS rate at 1 year was 65.1% (95% CI, 48.9 - 77.3). Among patients who achieved CR before the initiation of maintenance treatment, (d) DFS at 1 year was 85.7% (95% CI, 95.1 - 61.9) among the patients who achieved CR.

Treatment adherence and safety profile

Overall, 65.1% of patients (n=28) completed preplanned twelve cycles of TD maintenance. 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 of premature termination was an adverse event (n=6), followed by disease progression (n=4) and withdrawal of informed consent (n=3). Mean thalidomide cycle was 5.7 (range, 1 - 8 cycles) and mean relative dose intensity was 41.1% (range, 8.3 - 91.7 of total planned dose) among the patients who experienced early termination of the study whereas mean relative dose-intensity of thalidomide was 81.1% (range, 33.3 - 100.0) among the patients who completed the study. 18 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 adverse events. Detailed information of dose and schedule modification is presented in Table 3.

Table 3. Dose and schedule modification during trial

Cycle	Dose reduction (n=31)		Schedule delay (n=12)		Study termination (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)	1	Adverse event (infection) (1)
3	8	Adverse event (5) Investigator's decision (3)	2	Adverse event (1) Others (dental check) (1)		
4	5	Adverse event (4) Investigator's decision (1)	1	Adverse event (1)	2	Adverse event (hepatitis) (1) Disease progression (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			
8	1	Adverse event (1)	2	Adverse event (1) Others (patient schedule) (1)	4	Adverse event (neuropathy) (1) Disease progression (2) Treatment refusal (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	Treatment refusal (1)
12	1	Investigator's decision (1)	4	Adverse event (3) Others (patient schedule) (1)	2	Adverse event (neuropathy) (1) Investigator's decision (1)

Any AEs related to treatment occurred in 90.7% of the patients; AEs graded more than 3 occurred in 14 patients (32.6%). The most common AE was PN. During the total study period, 41.9% (n=18) of patients experienced PN, irrespective for the severity. With the dose modification by the protocol, the majority of the PNs were mild to moderate (n=18). However, 11.1% of the PN patients (n=2) discontinued treatment because of PN. Mean dose intensity of thalidomide received by these patients was 68.2% (range, 22.9 - 100.0) and the mean time elapsed between randomization and the onset of the adverse event 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. 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. A venous thromboembolic event occurred only in one patient. AEs occurred in more than 5% of patients are summarized in Table 4.

Table 4. Number (%) of patients with adverse events with an incidence of more than 5% during maintenance treatment

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 neuropathy	18 (41.9)	2 (4.7)
Dizziness	3 (7.0)	0 (0.0)
Endocrinologic		
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)

Prognostic factor analysis

Table 5 shows risk factor analysis for OS, EFS and PFS of entire patient population. The probability of OS was significantly lower among patients with unsatisfactory treatment response with first-line induction treatment (Hazard ratio [HR] 10.37; 95% CI, 1.15 - 93.44; p = 0.037). PFS was related to following clinical features: Bone marrow (BM) plasma cell infiltration exceeding 35% of total BM cells (HR 4.57; 95% CI, 1.24 - 16.76; p = 0.022), previous thalidomide exposure (HR 0.32; 95% CI, 0.11 - 0.95; p = 0.041) and unsatisfactory treatment response with first line induction treatment (HR 3.27; 95% CI, 1.09 - 9.81; p = 0.035).

Table 5. Risk factor analysis for OS, PFS and EFS

	OS			EFS			PFS		
	HR	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Male vs. female	1.54	0.17 – 13.83	0.701	0.70	0.28 – 1.76	0.449	1.16	0.36 – 3.80	0.806
Age ≥60	1.17	0.20 – 7.00	0.864	1.28	0.54 – 3.07	0.574	1.43	0.48 – 4.28	0.518
Anemia	3.95	0.65 – 23.86	0.134	2.60	0.94 – 7.20	0.067	**4.11**	**1.21 – 13.96**	**0.023**
LDH >UNL	1.45	0.24 – 8.69	0.688	1.75	0.68 – 4.54	0.247	0.79	0.24 – 2.59	0.696
B2MG >UNL	5.42	0.60 – 48.69	0.132	2.59	0.92 – 7.31	0.073	2.51	0.70 – 8.97	0.156
BM plasma cell >35%*	70.38	0.05 – 94531.03	0.247	1.77	0.72 – 4.34	0.214	**4.57**	**1.24 – 16.76**	**0.022**
Poor cytogenetics†	0.53	0.06 – 4.79	0.571	0.79	0.31 – 2.05	0.634	1.89	0.63 – 5.64	0.254
DSS III	1.83	0.31 – 10.99	0.507	0.90	0.38 – 2.15	0.816	0.36	0.12 – 1.14	0.081
ISS score II or III	1.84	0.31 – 11.06	0.506	0.88	0.37 – 2.10	0.776	1.00	0.34 – 3.00	0.996
Thalidomide exposure	0.21	0.04 – 1.27	0.090	0.75	0.29 – 1.93	0.546	**0.32**	**0.11 – 0.95**	**0.041**
< VGPR after ASCT	0.77	0.13 – 4.61	0.774	1.01	0.43 – 2.39	0.976	3.34	0.92 – 12.18	0.067
≥2 lines in induction	**10.37**	**1.15 – 93.44**	**0.037**	1.29	0.51 – 3.21	0.592	**3.27**	**1.09 – 9.81**	**0.035**

OS, overall survival; EFS, event-free survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; B2MG, beta-2 microglobulin; UNL, upper normal limit; BM, bone marrow; DSS, Durie-Salmon stage; ISS, international staging system; VGPR, very good partial response; ASCT, autologous stem cell transplantation

Discussion

This is a multicenter phase II trial to investigate the feasibility and tolerability of thalidomide maintenance therapy following ASCT in Korean patients. In this study, we used 100 mg of thalidomide and included patients who had been exposed to thalidomide or bortezomib prior to thalidomide maintenance. As the result, 1-year EFS was 65.1% and 2-year PFS and OS were 62.5% and 85.6%, respectively. Besides, considerable patients who failed to achieve CR with high dose chemotherapy and autograft showed improvement in their disease status with thalidomide maintenance. But even with relatively low dose of thalidomide compared with other randomized trials and limited maintenance duration of 12 months, toxicity was not ignorable, making 14% of patients (n=6) discontinue maintenance earlier than planned schedule.

Since mid-2000s, many investigators have published the result of randomized controlled trials on the concept of ASCT and thalidomide maintenance strategy after induction chemotherapy (13, 21-23). Studies consistently showed benefits in PFS, but they failed to show clear OS improvement. In 2016, Korean investigators reported real-world data about thalidomide maintenance, which showed similar outcome with previous randomized trials in that thalidomide therapy showed prolonged PFS but the result was not associated with improvement in OS (24). Although it is impossible to make a side-by-side comparison of these

studies with the current study, our result was also showed comparable survival outcome.

However, as expected, treatment adherence was not satisfactory mainly due to drug toxicity. PN was the most frequently encountered AE. PN occurred in 41.9% of patients and the proportion was predictable considering previous major studies. With dose adjustment, PN graded more than 3 was not frequent, but it was still a major concern in treatment halt and schedule delay. In contrast to the frequency of PN being similar to that of the western reports, the frequency of other complications including thromboembolic event was significantly low in Korean patients (25). All except one patient took aspirin, and none took an anticoagulant for thrombosis prophylaxis. In Korean patients, careful monitoring of neurologic complications is relatively critical for successful thalidomide maintenance treatment.

In risk factor analysis, previous treatment history was found to increase the risk of an event during maintenance therapy. And there appears to be PFS benefit in patients who had previous thalidomide treatment. This finding suggests that thalidomide maintenance may be a good therapeutic strategy in patients with good response with thalidomide as induction setting. And particularly, as was in one of the early trials, IFM 99-02, patients with less than VGPR after ASCT showed a tendency of benefit with thalidomide maintenance, suggesting that those who failed to achieve optimal response with most potent treatment can additionally be saved through this approach (13).

In contrast, poor cytogenetic feature, which was defined as t(4;14), t(4;16) and del(17) did not significantly affect the outcome of thalidomide maintenance. This finding is inconsistent with other reports indicating that thalidomide can be less effective in patients with poor cytogenetics (26). But generally, these findings are confined to subgroup analyses of major randomized trials. The association between cytogenetic feature and response to thalidomide maintenance is not fully defined yet, so these findings need to be validated with larger studies.

Novel treatments including lenalidomide and bortezomib are now widely used as maintenance in North America and Western Europe, but they are practically unavailable in many other countries due to several reasons. In Korea, the use of lenalidomide causes an additional cost of United States Dollars 1,300 per month compared with thalidomide, as national health care insurance does not cover lenalidomide maintenance. Furthermore, accessibility to novel agents is still limited in certain circumstances. For these reasons, it is often impossible to treat according to guideline although lenalidomide maintenance is the only category 1 maintenance treatment by the current guideline (10). Thus, in decision making for maintenance treatment of myeloma, long-term follow-up and real-world data on thalidomide maintenance still seem valuable.

Australian group reported updated survival data of ALLG MM6 trial and analyzed incremental cost-effectiveness of thalidomide maintenance (27). Considering life-year saved by thalidomide and many other social and clinical factors that

might affect to medical expense, the investigators concluded that thalidomide maintenance can be an effective strategy, especially when lenalidomide is not available. ~~And~~ Recently, there have been a couple of reports about survival updates of previous randomized trials. In contrast to previously publicized original articles, long-term follow-up result of Total Therapy 2 and HOVON-50, which adopted thalidomide from the start of the induction phase, reported benefits in OS with more than 5 years of long-term follow-up (28, 29). With these results, it is assured again that thalidomide maintenance can be a reasonable option when there is little option available. In light of the studies mentioned above, the result of current study also seems worthy of note.

There are some limitations in our study. Firstly, one of the major limitations of our study is its small patient population and lack of a comparator arm. Additionally, there was considerable heterogeneity among the patients in terms of previous treatment history and thalidomide exposure. Secondly, our study is limited by its short follow-up duration. Although there have been many studies to find the best surrogate endpoint in myeloma treatment (30, 31), a number of studies have reported long-term survival results that are not consistent with original reports. Lastly, the data on treatment outcome and survival after progression with thalidomide maintenance was not included in our current study. Several papers mentioned the effect of thalidomide on treatment after progression, with some evidence of short progression to death duration among thalidomide maintenance group (22, 23, 32). In this context, our data also needs

long-term follow up for comprehensive judgment of the value of the treatment.

In conclusion, our data showed Korean patients also benefitted with thalidomide maintenance, showing the comparable result with previous reports. Despite all the complications and unclear OS benefit, we cannot dismiss thalidomide maintenance with all these aforementioned data. As prolonged survival in myeloma patients is very promising with the development of new treatment strategies, maintenance will be more and more crucial in the myeloma treatment. A multidisciplinary approach with not only medical aspects but also the social aspects is highly required.

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국문초록

새롭게 진단된 다발골수종환자에서 자가조혈모세포이식후 탈리도마이드와 덱사메타손 유지요법에 대한 전향적 다기관 연구

김상아
서울대학교 대학원 의학과 중개의학

다발골수종의 치료 성적은 유지요법의 발전과 함께 향상되어 왔다. 비록 탈리도마이드는 부작용이 드물지 않으며 전체 생존율에 대한 연구 결과가 일관되지 않다는 제한점이 있기는 하지만 탈리도마이드는 면역조절제 중 가장 먼저 유지요법으로써 연구되었던 약제이며 한국에서 흔하게 사용되어 온 약제이다. 현재는 차세대 면역조절제와 단백체저하제가 새로운 유지요법으로 활발하게 연구되고 있기는 하지만, 실제 진료 현장에서는 비용 및 약제 접근성의 측면에서 이러한 새로운 약제의 사용이 제한적인 경우가 드물지 않으며 이러한 경우 탈리도마이드는 여전히 사용 가능한 선택지이다. 본 연구는 다발골수종으로 처음 진단되어 유도요법과 자가조혈모세포이식을 시행한 한국 환자들에서 탈리도마이드 유지요법의 효용성과 부작용에 대하여 확인하고자 하는 공개, 다기관 전향적 2상 연구이다.

본 연구에 등록된 환자들은 유도요법 및 자가조혈모세포이식 후 총 12주기 동안 탈리도마이드와 덱사메타손을 병합하여 투약 받았다. 각 주기는 28일로 구성되었으며 1주기의 치료 당 탈리도마이드는 100 mg을 28일 동안, 덱사메타손은 40 mg을 4일 동안 투약하였다. 연구의 일차 목적은 시험약 투약 시작 후 1년 시점의 무사건

생존율이었으며, 이는 질병의 재발, 진행, 심각한 독성으로 인한 치료 중단 혹은 원인과 관계없이 사망하는 경우로 정의하였다. 이외에도 무진행 생존율, 전체 생존율 및 안전성에 대하여도 조사하였다.

2013년 7월부터 2015년 11월까지 한국의 7개 의료 기관에서 총 43명의 환자가 등록되었다. 전체 환자의 중앙 추적 관찰 기간은 17.3개월 (범위, 1.1 – 32.2)이었다. 이 중 33명 (76.7%)의 환자만이 계획한 12주기의 유도요법을 모두 완료하였으며, 치료를 도중에 중단한 환자에서 치료 유지 기간의 중앙값은 5.6개월 (사분위범위, 2.9 – 6.9)이었다. 전체 환자에서 1년 무사건 생존율은 65.1% (95% 신뢰구간, 48.9 – 77.3) 이었으며 1년 무진행 생존율은 85.6% (95% 신뢰구간, 70.7 – 93.3), 1년 전체 생존율은 90.4% (95% 신뢰구간, 96.3 – 76.3)이었다. 자가조혈모세포이식 후 완전반응을 얻지 못했던 환자들 중, 4명의 부분반응 환자와 3명의 우수부분반응 환자가 유도요법을 받으면서 완전반응을 획득하였다. 무사건 생존율에 대한 단변량 분석에서는 생존율에 유의하게 영향을 주는 임상적 요소를 확인하지 못하였으나, 무진행 생존율에 대한 단변량 분석에서는 유도요법에서부터 탈리도마이드가 포함된 요법을 투약 받은 환자군이 우월함을 확인하였다 (위험도, 0.32; 95% 신뢰구간, 0.11 – 0.95; p = 0.041). 다만, 전체 환자 중 39명이 (90.7%) 유지요법 중 부작용을 경험하였고, 3단계 이상의 독성을 경험한 환자는 14명 (32.6%)이었다. 탈리도마이드의 가장 흔한 부작용 중의 하나로 알려진 말초신경병증은 20명 (46.5%)의 환자에서 발생하였으며, 말초신경병증이 발생한 경우 탈리도마이드의 용량을 조절하기는 하였으나 여전히 약제 중단을 야기하는 부작용 중 가장 흔한 원인으로 작용하였다.

요약하자면 한국 환자에서 탈리도마이드 유지요법에 대하여 연구한 본 연구에서 탈리도마이드유지요법은 기존의 보고와 비슷한 정도의 효용성을 보였으나, 상당한 수의 환자가 약제 관련 부작용을 경험하였으며 이는 유지요법을 중단하게 하는 주된 요인이 되었다.

결론적으로, 레날리도마이드와 같은 새로운 약제를 사용하기 어려운 상황에서, 탈리도마이드 유지요법은 고려해 볼 수 있는 효과적인 치료 중 하나이지만, 치료 중 말초신경병증과 같은 약제 부작용에 각별히 유의하여야 한다.

중심어: 다발골수종, 탈리도마이드, 유지요법, 자가조혈모세포이식

학번: 2017-21290