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Safety of lenalidomide, dexamethasone, and cyclophosphamide in elderly Japanese patients with relapsed and refractory multiple myeloma: results of phase 1 study

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The RCd regimen (lenalidomide [LEN]-cyclophosphamide [CY]-dexamethasone [DEX]) was effective and well-tolerated in relapsed and refractory multiple myeloma (RRMM) European patients aged between 59 and 65 years. However, most Japanese myeloma patients are over 70 years old. Thus, we analyzed the safety of RCd therapy in a phase 1 study of elderly Japanese RRMM patients aged >70 years (median age 76 years). CY was administered to three cohorts of three patients each at 200, 300, and 400 mg on days 1, 8, and 15 of a 28-day cycle with DEX (40 mg on days 1, 8, 15, and 22) and LEN (15 mg on days 1–21) for a maximum 8 cycles. One patient receiving 200 mg CY developed thrombocytopenia (Gr.4) and pneumonia (Gr.3). Two patients each developed neutropenia (Gr.4) at 300 mg and skin rash (Gr.3) at 200 mg. No severe adverse events were observed. Maximum tolerated dose of CY was determined to be 400 mg. After 2 cycles, the overall response rate was 88.9%. After a median follow-up of 36.4 months, median duration of response, progression-free survival, and overall survival were 8.3, 10.6, and 36.4 months, respectively. (UMIN Clinical Trials Registry number, UMIN000009391).

Key words: relapsed and refractory multiple myeloma, cyclophosphamide combination therapy, RCd regimen

Introduction

Multiple myeloma (MM) is a B-cell neoplasm that causes various symptoms, such as osteolytic bone lesion, anemia, and renal failure, as a result of the proliferation of monoclonal plasma cells in the bone marrow and the increase in M-protein that they produce. Recently, novel agents such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies have been successfully approved, improving prognosis for myeloma patients. However, this malignancy is still difficult to cure outright. Therefore, clinical trials have been conducted to investigate the efficacy of new treatment regimens including these novel agents for relapsed and refractory multiple myeloma (RRMM).

Three European groups reported positive outcomes and tolerable toxicity when treating RRMM with a combination regimen of lenalidomide (LEN), cyclophosphamide (CY), and steroids [1–3]. Using such treatment regimens comprising only oral drugs provide additional advantages in reducing hospital visits, maintaining existing lifestyles, and allowing patients to continue working. The median age in these studies was relatively young (59 to 66 years old) compared to the approximately 65% of patients with MM in Japan who are elderly individuals aged 70 years and older according to the static data of the National Cancer Center Japan [4]. Due to this discrepancy in the age distribution of the clinical trial patients and the primary target population, these treatment doses and schedules may not be suitable for treating MM in Japan.

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Therefore, we planned a phase 1/2 clinical trial to investigate the safety and efficacy of RCd therapy (LEN-CY-dexamethasone [DEX]) in elderly Japanese RRMM patients aged 70 years and older, and we herein report the results of the completed phase 1 portion (RefLEX study, UMIN Clinical Trials Registry number, UMIN000009391).

Methods

Patients

The study included Japanese patients aged ≥70 years with symptomatic MM, as diagnosed using the International Myeloma Working Group (IMWG) criteria [5], who had received at least one prior treatment regimen. Patients had a Karnofsky performance status (KPS) score of greater than 70% or an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 (cases of PS 2–3 due to bone lesion or fracture were allowed to be registered); adequate bone marrow function (defined as platelet count >50 × 10^9/L, hemoglobin concentration >7.0 g/dL, and absolute neutrophil count 1.0 × 10^9/L); alanine aminotransferase and aspartate aminotransferase ≤2 × the upper limit of normal, and total bilirubin ≤2.0 mg/dL; serum creatinine <2.0 mg/dL; adequate cardiac function (defined as left ventricular ejection fraction ≥50%, and no findings of QT prolongation (<450 ms), atrial fibrillation or ventricular arrhythmia in electrocardiogram); no abnormal shadow in both lung fields on the chest X-ray; no severe peripheral neuropathy, neuropathic pain and functional loss (<grade 2). Furthermore, male patients agree to contraception by one or more appropriate methods during treatment.

Exclusion criteria included: previous treatment with lenalidomide; complication of systemic amyloidosis; other malignancies within 5 years of initiating study treatment; arrhythmia with treatment; history of myocardial infarction, angina pectoris, cerebral infarction or arterial/venous thrombosis; hepatic cirrhosis; requiring hemodialysis; active infection; infection with human immunodeficiency virus or active hepatitis B or C virus; severe mental disorders such as schizophrenia; or use of major tranquilizer, antidepressant, or antimanic drugs.

This study was approved by the institutional review board or independent ethics committee at each participating institution and was conducted in accordance with the principles for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Study design and treatment

The study was designed as a phase 1/2 study and conducted by the Kanto-Tohoku Multiple Myeloma Conference (KTMM) in Japan. The primary endpoints of the phase 1 trial were the maximum tolerated dose (MTD) of the RCd regimen, the incidence of adverse events, and the duration of therapy. The secondary endpoints were the best response rate, duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC), version 4.0 after the second cycle of RCd therapy. This study used a standard 3 + 3 design to evaluate MTD. If none of the first three patients developed dose-limiting toxicity (DLT), a further three patients would be enrolled at the next dose level. If one or two patients in each dose level developed DLT, an additional three patients were registered at the same level. If only one or two of six patients developed DLT, three patients were enrolled at the next dose level. If three or more of six patients had developed DLT, the external safety monitoring committee would have reconsidered the continuation of this study. If treatment-related death occurred, registration would be immediately stopped upon submission of a severe adverse event report and the external safety monitoring committee would discuss the potential discontinuation of the study.

DLT included: grade 4 hematologic toxicity lasting 7 days or more; any non-hematologic toxicity of grade 4 or higher except myeloma and myeloma-treatment associated symptoms, such as cataracts, skin lesions, gastritis, diarrhea, hypercalcemia, hyperglycemia, polyneuropathy and infections (including pneumonia); a delay of more than 29 days between courses of RCd therapy due to adverse events; and patient refusal due to toxicity. The external safety monitoring committee assessed the appropriate response according to the International Myeloma Working Group (IMWG) criteria [6].

Patients were enrolled in 3 dosing cohorts. The dosage regimes followed an escalation protocol as shown below: Level 1: CY 200 mg + LEN 15 mg + DEX 40 mg, Level 2: CY 300 mg + LEN 15 mg + DEX 40 mg, Level 3: CY 400 mg + LEN 15 mg + DEX 40 mg. CY was orally administered on days 1, 8, 15 (or 22) of each 28-day cycle. LEN (15 mg initially, then adjusted depending on each patient's renal function) was orally administered daily for the first 21 days and DEX was orally administered on days 1, 8, 15, and 22. LEN was discontinued if the patient developed grade 3 or 4 peripheral neuropathy and skin lesions, as indicated by the package insert. Patients underwent a maximum of 8 RCd treatment cycles. Patients were allowed to undergo LEN maintenance therapy. Concurrent thromboembolism prophylaxis was required and prophylaxis for *Pneumocystis jirovecii* pneumonia and varicella-zoster virus infection was recommended. Transfusion and the use of granulocyte-colony stimulating factors (G-CSF) were also allowed, if necessary.

Results

Patient characteristics

Between January 2013 and December 2015, 10 elderly Japanese patients with RRMM were enrolled in 3 hospitals. One patient was subsequently excluded from the study as the dose of LEN for this patient was supposed to be attenuated according to their renal function and the external safety monitoring committee concluded that this case was not suitable for the evaluation of safety. The nine remaining patients were included in the safety and efficacy analyses. The characteristics and treatment outcomes of patients are shown in Table 1. The median age of the 9 patients (4 males and 5 females) was 76 (range: 70–80). The median number of prior treatment therapies was 2 (range: 1–4). Eight patients had previously received bortezomib-containing regimens and 2 patients had received thalidomide-containing regimens. No patients had undergone autologous stem cell transplantation.

Initially, a phase 1/2 study was planned. However, we encountered difficulty in enrolling enough patients to properly evaluate the efficacy of RCd therapy in a phase 2 trial. Furthermore, several novel agents that showed favorable treatment outcomes for RRMM were clinically approved after the initiation of this study. Thus, the study was halted following completion of the phase 1 trial.

MTD and safety of RCd

All 9 evaluated patients received at least 2 cycles of RCd therapy (median: 3 cycles; range: 2–8) and none experienced DLT at any of the tested dose levels. Adverse events are shown in Table 2. At dose level 1 (200 mg CY), one patient (#1-2) developed pneumonia (grade 3) at day 33 of cycle 1 and thrombocytopenia (grade 4) at day 18 of cycle 2. This patient was treated with antibiotic and antifungal agents and recovered from pneumonia. Thrombocytopenia was improved following discontinuation of LEN. Another patient (#1-3) developed skin rash (grade 3) at 200 mg CY and improved following interruption and dose reduction of LEN. At dose level 2 (300 mg CY), one patient (#2-1) experienced anemia (grade 3) at day 7 of cycle 2 and neutropenia (grade 4) at day 20 of cycle 2. This patient required red blood cell transfusion and G-CSF. After 2 cycles, she reached partial response (PR) and started LEN maintenance therapy. At dose level 3 (400 mg CY), no patients developed grade 3 or 4 adverse events. The MTD of CY was thus determined to be 400 mg.

Seven of the patients received LEN maintenance therapy following the RCd regimen. The median duration of therapy of RCd and LEN maintenance was 11.6 months (range: 2.1–56.2 months). One patient (#2-3) is currently undergoing ongoing LEN maintenance therapy (duration of therapy: 56 weeks).

Efficacy of RCd

All 9 patients were evaluated for response to treatment with RCd therapy. After 2 cycles of RCd therapy, the overall response rate (ORR) was 88.9% (8 of 9 patients). Eight patients achieved very good partial response (VGPR) or partial response (PR), including 3 patients with high-risk cytogenetic abnormalities including t(4;14) and del 17p (Table 1). At the median follow-up of 36.4 months (range: 21.5–57.5), the median DoR, PFS, and OS were 8.3, 10.6, and 36.4 months, respectively.

Discussion

CY is still a useful and inexpensive agent for myeloma therapy. The safety and efficacy of combination therapies with CY and novel agents is well known. In the latest National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2019) [7], 4 CY-containing regimens, including PCD (pomalidomide-CY-DEX), BCD (bortezomib-CY-DEX), and KCD (carfilzomib-CY-DEX), are recommended as therapy for newly diagnosed MM (NDMM) or RRMM. The guidelines also recommend the RCd regimen as "useful in certain circumstances" for primary therapy of non-transplant candidates and is included among "other recommended regimens" for previously treated MM patients. Although the RCd regimen was first reported more than ten years ago, its effectiveness is still being studied and reported. Of the three RCd therapy studies previously reported [1, 2, 8], one was a phase 1/2 study of its use in treatment of RRMM [2]. Patients in this study had a median age of 65 (range: 42–79) and had undergone a median of 3 previous lines of treatment (range: 1–6). Following evaluation after the first 28-day cycle of RCd, the MTD was fixed at 600 mg of CY administered on days 1 and 8, daily administration of 25 mg of LEN for the first 21 days, and 20 mg of DEX administered on days 1–4 and 8–11. The MTD for the overall cycle was the same as that found in our study (1,200 mg CY and 160 mg DEX). However, our study used a lower dose of LEN. Eight of the 31 patients (26%) in the European phase 1/2 trial required a lower dose of LEN due to adverse events, while only one case (#1-3) required dose attenuation in our study.

According to the data of National Cancer Center Japan, the number of elderly patients with MM has been significantly increasing in Japan [4], so the frailty and comorbidity of patients must be taken into consideration during myeloma therapy. The European Myeloma Network and IMWG have provided scoring systems and dose modification recommendations for the use of chemotherapeutic agents in frail, elderly patients [9, 10]. For 'fit' patients, the doses recommended were 25 mg of LEN on days 1–21, 300 mg/m^2 of CY on days 1, 8, and 15, and 40 mg of DEX on days 1, 8, 15, and 22, and for 'unfit' patients, the recommended doses were 15 mg,

Table 1. Baseline characteristics and therapeutic outcomes of patients treated with the RCd regimen

Dose level 1			
Patient number	#1-1	#1-2	#1-3
Age/Gender	70/male	79/female	74/male
ECOG PS	0	0	0
Geriatric assessment*	Fit	Unfit	Fit
M-protein	IgG-λ	IgG-λ	IgG-κ
DSS/ISS	IIIA/II	IIA/I	IIIA/II
Cytogenetic abnormalities	t(4;14)**	No	t(4;14)**, Hyperdiploidy
Previous lines of treatment	1	2	1
Prior treatment (cycles)	BD (11), MPB (5)	BD (8) and bortezomib maintenance, MPB (8)	BD (7)
RCd cycles	8	3	8
LEN maintenance (Dose)	Yes (10 mg daily)	Yes (10 mg daily)	Yes (10 mg daily)
Adverse events	No	Pneumonia (G3) Thrombocytopenia (G4)	Skin rash (G3)
Best response	PR	PR	PR
Dose level 2			
Patient number	#2-1	#2-2	#2-3
Age/Gender	80/female	76/female	80/female
ECOG PS	1	3 (bone lesion)	0
Geriatric assessment*	Unfit	Frail	Unfit
M-protein	IgA-κ	IgG-κ	IgG-κ
DSS/ISS	IIIA/III	IIIA/II	IIA/II
Cytogenetic abnormalities	Del 17p**, t(4;14)**	No	No
Previous lines of treatment	3	2	2
Prior treatment (cycles)	MP (1), BD (5), BD re-treatment (5)	MP (4) and thalidomide maintenance, MPB (4)	HDD, MPT (7) and thalidomide maintenance
RCd cycles	2	2	5
LEN maintenance (Dose)	Yes (10 mg)	No	Yes (5 mg) ***
Adverse events	Anemia (G3), Neutropenia (G4)	Neutropenia (G1), Pharyngitis (G1)	Peripheral neuropathy (G2)
Best response	PR	PR	VGPR
Dose level 3			
Patient number	#3-1	#3-2	#3-3
Age/Gender	73/female	73/male	76/male
ECOG PS	1	1	0
Geriatric assessment*	Fit	Fit	Unfit
M-protein	LC-λ	LC-λ	IgA-κ
DSS/ISS	IIIA/III	IIIB/III	IIIB/III
Cytogenetic abnormalities	No	No	No
Previous lines of treatment	2	1	4
Prior treatment (cycles)	ROAD (8), BD (10)	BD (4) and bortezomib maintenance	VAD (4), MP (15), BD (7), BD re-treatmment (10)
RCd cycles	2	2	4
LEN maintenance (Dose)	No	Yes (10 mg)	Yes (5 mg)
Adverse events	Peripheral neuropathy (G2) Upper respiratory infection (G2)	No	No
Best response	SD	PR	PR

*patients were classified as 'Fit', 'Unfit', or 'Frail' according to the IMWG proposed scoring system [10].
**fluorescent *in situ* hybridization (FISH) analysis.
***ongoing.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; DSS, Durie and Salmon staging system; ISS, International Staging System; LEN, lenalidomide; LC, light chain; BD, bortezomib and dexamethasone; MPB, melphalan, prednisolone, and bortezomib; MP, melphalan and prednisolone; HDD, high-dose dexamethasone; MPT, melphalan, prednisolone, and thalidomide; ROAD, ranimustine, vincristine, melphalan, and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; PR, partial response; VGPR, very good partial response; SD, stable disease.

Table 2. Adverse events observed in patients treated with the RCd regimen

Adverse event, *n* (%)	All grade	Grade 3/4
Anemia	1 (11.1)	1 (11.1)
Thrombocytopenia	1 (11.1)	1 (11.1)
Neutropenia	2 (22.2)	1 (11.1)
Peripheral neuropathy	2 (22.2)	0 (0.0)
Skin rash	1 (11.1)	1 (11.1)
Pharyngitis	1 (11.1)	0 (0.0)
Upper respiratory infection	1 (11.1)	1 (11.1)
Pneumonia	1 (11.1)	1 (11.1)

150 mg/m^2, and 20 mg. The MTDs of RCd therapy in our study were approximately equal to these recommended doses and are therefore considered to be appropriate for elderly Japanese patients with RRMM.

The RCd regimen is composed entirely of orally administered drugs, which reduces frequency of hospital visits and duration of hospital stay. This is a major benefit for patients with bone disease, disability, and comorbidity, and who live far from hospitals. Additionally, triplet combinations have been recommended for patients with RRMM, because they have produced more favorable outcomes than doublet regimens [11]. The NCCN guidelines proposed 33 treatment regimens for RRMM [7]. Of these, two triplet combination therapies consisting only of orally administered drugs are approved in Japan: the IRD (ixazomib [IXA]-LEN-DEX), and RCd therapies. The efficacy of IRD was evaluated in a phase 3 TOURMALINE-MM1 trial [12]. The median age and previous lines of treatment undergone by patients were 66 (range: 38–91) and 1 (range: 1–3), respectively. The ORR was 78% and 2-year PFS was around 50%. Any and grade 3 or 4 adverse events were observed in 98% and 74% of patients, respectively. In the previously described phase 1/2 RCd study [2], the ORR was 81% and 2-year PFS was 56%. Grade 3 or 4 complications occurred in 19% of patients. Comparing patient characteristics in these 2 studies, age was consistent, while the number of previous lines of regimens was larger in the RCd group than in the IRD group. Based on these outcomes, it seems that the RCd regimen has a lower incidence and lower grade of adverse events than IRD therapy. Additionally, the MTD of our study is lower than that reported in a previous RCd study. Thus, our RCd regimen may be safer and better tolerated in elderly RRMM patients.

The majority of novel agents are very expensive, leading to increasing economic burden on patients with time. The cost of chemotherapeutic agents in RCd therapy (about 0.6 million yen per cycle) is significantly more inexpensive than in IRD therapy (about 1.47 million yen per cycle). Recently, 'financial toxicity,' referring to the increased financial burden associated with cancer treatment that adversely affects a patient's quality of life, has become recognized as a global issue [13]. Although several public medical health insurance systems cover almost all Japanese people, some patients with colorectal cancer have been unable to receive the most appropriate treatment due to economic reasons [14]. In general, the cost-effectiveness of drugs and treatment should be evaluated using the quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER). A recent study showed that the IRD regimen had a higher ICER than other novel agent-based regimens for the treatment of MM [15]. As we did not evaluate the QOL and cost of the therapy, it was impossible to analyze the cost-effectiveness of our RCd regimen. However, because of the low price of CY, its use in combination regimens does not significantly increase the cost of these therapies. Thus, the RCd regimen may be a viable option for affordable treatment of RRMM.

All things considered, we think that RCd therapy is a safe and reasonable option for the treatment of elderly Japanese RRMM patients.

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Conflict of Interest

Makoto Sasaki received honoraria for lectures from Celgene, Takeda Pharmaceutical, and Janssen. Hideto Tamura discloses receipts of honoraria for lectures from Bristol-Myers Squibb, Celgene, Ono Pharmaceutical, Takeda Pharmaceutical, and research grant from Celgene. Hiroshi Handa received honoraria and research grant from Celgene. Norio Komatsu has received a consulting fee from Celgene. The remaining authors declare that they have no conflicts of interest.

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