Therapeutic Outcome of Lenalidomide-dexamethasone in Patients with Relapsed or Refractory Systemic Immunoglobulin Light Chain (AL) Amyloidosis : A Single-center Analysis and Review of the Literature

Akihiro Ueno[1], Nagaaki Katoh[1]*, Naoki Ezawa[1]
Tsuneaki Yoshinaga[1], Masahide Yazaki[2)3)] and Yoshiki Sekijima[1]

1) *Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine*
2) *Institute for Biomedical Sciences, Shinshu University*
3) *Clinical Laboratory Sciences Division, Shinshu University Graduate School of Medicine*

Objective : To report the safety and efficacy of the lenalidomide-dexamethasone (Rd) regimen for previously treated patients with immunoglobulin light chain (AL) amyloidosis patients in a real-world clinical practice setting at a single amyloidosis center in Japan.

Methods : Clinical data about patient background characteristics and treatment outcomes of patients with previously treated systemic AL amyloidosis who received Rd as salvage treatment at our department were retrospectively collected and analyzed.

Patients : Among the total of 262 AL amyloidosis patients in a single institute, 22 patients who were treated with the Rd regimen between September 2001 and December 2019 after one or more preceding chemotherapeutic regimens fulfilled the inclusion criteria.

Results : The median follow-up period was 41 (range 1-68) months. The median number of previous treatment regimens was 2 (range 1-4). The numbers of patients who achieved complete response, very good partial response, partial response, and no response were 14 (64 %), 0 (0 %), 2 (9 %), and 6 (27 %), respectively. Eight patients (36 %) experienced grade≥3 adverse events. Toxicity-related treatment discontinuation occurred in four patients (18 %). No treatment-related mortality occurred. Four patients died during the observation period, three of whom died due to disease progression. The median overall survival has not yet been reached.

Conclusion : In this study, Rd was shown to be a safe and efficient treatment option for AL amyloidosis patients who were refractory to first-line therapy. These results provide an important insight for clinicians treating AL amyloidosis patients in a real-world clinical practice setting. *Shinshu Med J 70 : 29—38, 2022*

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Key words : dexamethasone, immunoglobulin light chain (AL) amyloidosis, lenalidomide, relapsed/refractory patients, treatment

I Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is one of the major types of systemic amyloidosis caused by pathogenic plasma cell clones in the bone marrow. These clonal cells produce aberrant light chains in an unregulated manner, which accumulate and are deposited as amyloid fibrils in multiple vital organs, such as the kidney, heart, and liver, where they cause serious functional damage[1)-3)]. Therefore, the fundamental treatment strategy for

* Corresponding author : Nagaaki Katoh
Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : nagaaki@shinshu-u.ac.jp

AL amyloidosis involves eliminating these culprit plasma cell clones using chemotherapeutic agents. In 1998, high-dose melphalan with stem cell transplantation (HDM) was first reported to be effective for AL amyloidosis[4], and is now considered one of the first-line treatment options[5)6)]. Recently, new chemotherapeutic drugs with a novel antineoplastic mechanism of action, the proteasome inhibitors (PI), have emerged and are now considered as major options in the treatment of AL amyloidosis[5]. Bortezomib is a PI that was first reported to provide good treatment outcomes in patients with AL amyloidosis in 2007[7], and it has been widely adopted in Japan[3] and around the world[5]. In a recent study, we demonstrated its favorable efficacy in AL amyloidosis, including 65 % of untreated newly diagnosed patients[8]. However, a proportion of patients do not respond to these front-line therapies or subsequently relapse, and it is therefore very important to investigate salvage treatment options for those who have relapsed or have refractory AL amyloidosis. Lenalidomide is one of the immunomodulatory drugs (IMiDs) that was shown to have efficacy in relapsed/refractory AL amyloidosis patients combined with dexamethasone (Rd regimen) in three prospective clinical trials[9)-11)]. However, the efficacy of Rd has not been described in detail outside of clinical trials, with only one retrospective observational study in the literature[12], so it is important to clarify the actual availability of the Rd regimen in actual clinical practice. Here, we report the safety and efficacy of the Rd regimen for previously treated AL patients in a real-world clinical practice setting at a single amyloidosis center in Japan. A literature review and comparison between previous reports and this study were also carried out.

Ⅱ Patients and Methods

A Patients

A total of 262 patients with systemic AL amyloidosis were identified in a series of medical records of our department between September 2001 and December 2019 at the Shinshu University School of Medicine, Matsumoto, Japan. Diagnosis of systemic AL amyloidosis was made based on light chain-derived amyloid deposition confirmed by immunohistology[13] and/or mass spectrometry[14] with evidence of an underlying monoclonal plasma cell population, such as positive immunofixation test for M protein and/or abnormal elevation of serum free light chain (FLC) and/or abnormal plasma cell population in the bone marrow on flow cytometric analysis.

Patients who were treated with Rd after one or more preceding chemotherapeutic regimens were retrospectively enrolled in this study. Those who were receiving ongoing Rd treatment without confirmed best hematological response at the time of registration were excluded. Patients with low involved FLC (iFLC) titer (＜100 mg/L), referred to as patients with hematologically "unmeasurable" disease[9], were also included in this study because the majority of previously treated patients had a decreased FLC level due to prior chemotherapy.

For evaluation of patient backgrounds, the international consensus guidelines from the 10th International Symposium on Amyloidosis[15] and Mayo Clinic staging system 2012[16] were used to determine organ involvement and clinical stage, respectively.

B Treatment

The regimen consisted of several cycles of lenalidomide at a dose of 20 mg/day or less for 21 days followed by 7 days of rest with dexamethasone at 40 mg/day or less on days 1-4 and 15-18[9]. Both were given orally. Drug doses were determined by the attending physician based on tolerance. The standard starting dose of lenalidomide at our center was 5 mg/day (a lower dose was applied in patients under dialysis) and then increased up to the maximum tolerable dose≤20 mg/day. Dexamethasone was started at a dose of 40 mg/day (20 mg/day or less in elderly patients (approximately more than 70 years old)) and decreased down to the tolerable dose. Patients received prophylaxis with low-dose aspirin (100 mg/day) and proton pump inhibitor.

Treatment cycles were continued until confirmation of best hematological response. If complete hematological response (CR) was achieved, several cycles (0-6 cycles) were added for consolidation if tolerated. Rd treatment was discontinued upon severe

Table 1　Clinical backgrounds of 22 patients at baseline

Variable	Value
Median age, years (range)	64.5 (48–82)
Number of male/female patients	10 / 12
Clonal subtype of cases, κ/λ, number (%)	6 (27.3) / 16 (72.7)
Number of cases previously treated (%)	22 (100.0)
Median number of previous treatment regimens (range)	2.0 (1–4)
Details of prior regimens, number of cases (%)	
Bortezomib and dexamethasone	21 (95.5)
Melphalan and dexamethasone	11 (50.0)
High-dose melphalan with stem cell transplantation	3 (13.6)
Vincristine, doxorubicin and dexamethasone	3 (13.6)
Lenalidomide or pomalidomide based regimen	0 (0.0)
Thalidomide	1 (4.5)
High dose dexamethasone	1 (4.5)
Median NYHA class (range)	1.0 (0–3)
Median ECOG performance status (range)	0.0 (0–3)
Mayo stage 2012, number of cases (%)	
Ⅰ	8 (36.4)
Ⅱ	5 (22.7)
Ⅲ	8 (36.4)
Ⅳ	1 (4.5)
Median dFLC, mg/L (range)	17.8 (2.60–506.92)
Median TnT, ng/mL (range)	0.041 (0.004–0.586)
Median NT-proBNP, pg/mL (range)	1584.0 (59.1–16203.0)
Organ involvement, number of cases (%)	
Heart	13 (59.1)
Kidney	18 (81.8)
Liver	6 (27.3)
Gastrointestinal tract	4 (18.2)
Peripheral nerve	2 (9.1)
Median of mean left ventricular wall thickness, cm (range)	1.45 (0.76–2.10)
Median left ventricular ejection fraction, % (range)	74.1 (44.4–88.9)
Median serum creatinine level, mg/dL (range)	1.01 (0.49–8.72)
The number of patients with advanced renal failure requiring dialysis (%)	2 (9.1)
Median urine protein/creatinine ratio, g/gCr (range)	3.08 (0–18.88)
Median total bilirubin level, mg/dL (range)	0.51 (0.26–2.31)
Median alkaline phosphatase level, IU/L (range)	303.5 (96–1794)

NYHA New York Heart Association, *ECOG* Eastern Cooperative Oncology Group
dFLC difference between involved and uninvolved free light chain, *TnT* troponin T
NT-proBNP N-terminal of the prohormone brain natriuretic peptide

adverse events or evidence of failure to response determined by continuous elevation or sustained nadir of iFLC before achieving CR.

C　Outcome evaluation

Hematological response was classified into four levels according to the international consensus guidelines, i.e., complete response (CR, normal FLC ratio with negative serum and urine immunofixation), very good partial response (VGPR, difference between involved and uninvolved FLCs (dFLC)＜40 mg/L), partial response (PR, dFLC decrease＞50 %), and no response (NR)[17]. However, these criteria are difficult to apply simply to previously treated patients with low FLC levels (so-called “unmeasurable” patients). For example, those with a decreased dFLC level＜40 mg/L at the Rd treatment baseline are unsuitable to determine a VGPR response. Therefore, we applied modified criteria as follows. If the baseline iFLC level was≥50 mg/L and＜100 mg/L, VGPR was not defined for those patients and only the CR, PR, or NR classification was applied. If the baseline iFLC level was＜50 mg/L, VGPR and PR were not defined for those patients and only the CR or NR classification was applied.

Some patients were treated with a second Rd regimen when they relapsed after completing the first

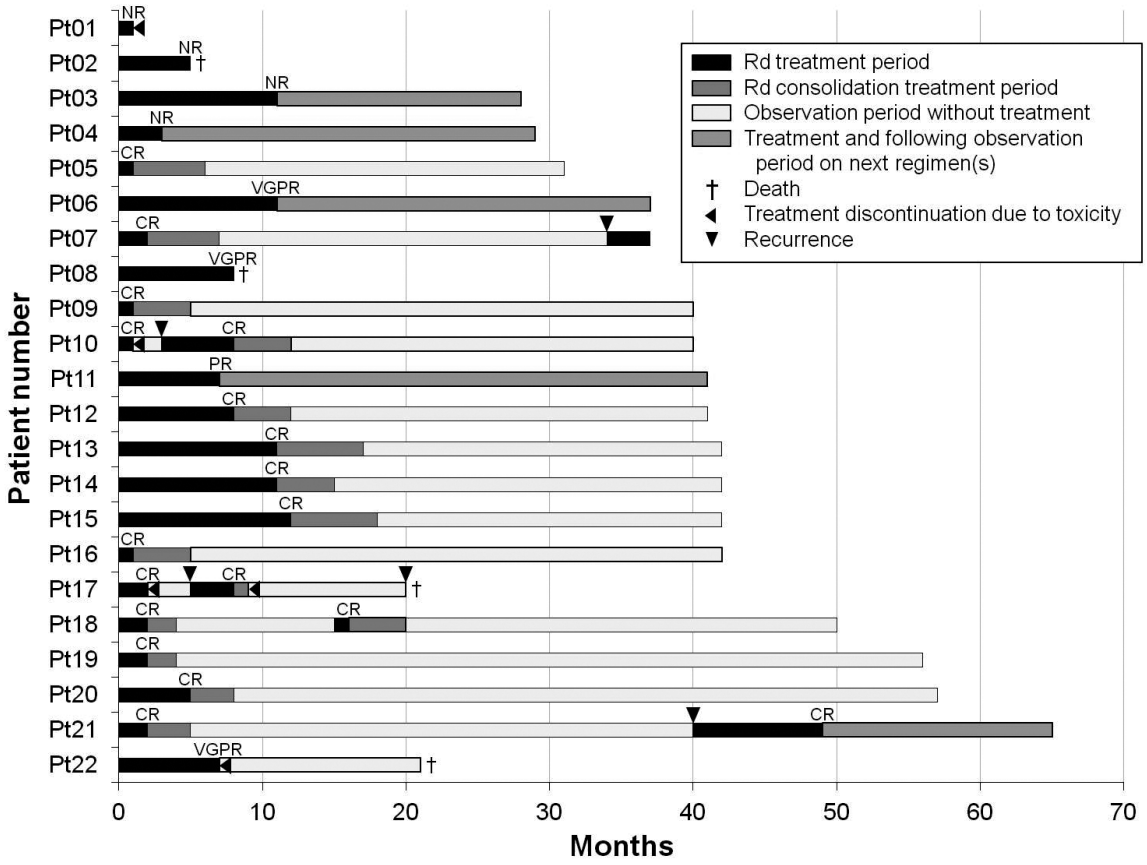

Fig. 1　Clinical courses of enrolled patients

Each bar represents an individual patient. The bar length indicates follow-up period. The meanings of symbols and colors of bars are indicated in the inset. A total of 22 patients are shown. Hematological response of each patient is presented on the bar.

Rd treatment. The results of hematological response for the second Rd regimen were excluded from calculating the best hematological response rate.

Adverse events were determined and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0-JCOG. Treatment-related mortality (TRM) was defined as early death within 100 days after initiation of treatment. Survival was evaluated by the Kaplan -Meier method.

Ⅲ　Results

A　Patient background

A total of 22 patients fulfilled the inclusion criteria and were enrolled in this study. The clinical backgrounds of these 22 patients at the Rd initiation baseline are summarized in **Table 1**. The median age of the patients was 64.5 (range 48-82) years. All patients had a prior treatment history as part of the inclusion criteria. The median number of previous treatment regimens was 2 (range 1-4). The most commonly used regimen before Rd was bortezomib-based therapy (bortezomib-dexamethasone)[8] (21 patients, 96 %). Three patients (14 %) were treated with HDM. There were no patients who had been previously exposed to IMiDs with the exception of one patient who had been treated with thalidomide (Pt21, **Fig. 1**). The most commonly involved organ was the kidney (18 patients, 82 %) and two patients had advanced renal failure requiring dialysis (Pt14 and 16, **Fig. 1**). Thirteen patients (59 %) had cardiac involvement and the median NYHA class was 1 (range 0-3), including three patients with NYHA class 3 (Pt04, 08, and 17, **Fig. 1**). According to the Mayo staging system 2012[16], 13 patients (59 %) were classified as less than stage III and there was only one patient with stage IV disease (Pt13, **Fig. 1**). The median iFLC and dFLC levels were 36.8 (range 12.2-

Table 2 Treatment details and outcomes

Parameter	Value
Median follow-up period, months (range)	41 (1-68)
Lenalidomide dose	
Median initiating dose, mg (range)	5.0 (2.5-5.0)
Median maximum dose, mg (range)	10.0 (2.5-20)
Median ending dose, mg (range)	7.5 (0.71-20)
Dexamethasone dose	
Median initiating dose, mg (range)	40 (8-40)
Median ending dose, mg (range)	20 (0-40)
Median number of total Rd treatment cycles (range)	6.5 (1-18)
Best hematological response, number (%)	
CR	14 (63.6)
VGPR	0 (0.0)
PR	2 (9.1)
NR	6 (27.3)
Median number of cycles needed to achieve ≥ PR (range), n=16	1 (1-7)
Median number of cycles needed to achieve CR (range), n=14	2 (1-12)
Median number of consolidation treatment cycles after achieving CR (range), n=14	4 (0-6)
Recurrence	
Recurrence among those achieving CR, number (recurrence rate, %), n=14	5 (35.7)
Median duration from achieving CR to recurrence, months (range), n=5	12 (2-35)
Tolerance	
The number of patients who discontinued Rd treatment due to toxicity (%)	4 (18.2)
Treatment-related mortality, number (%)	0 (0.0)

CR complete response, *VGPR* very good partial response, *PR* partial response, *NR* no response
Rd lenalidomide and dexamethasone

516.0) and 17.8 (range 2.6-506.9) mg/L, respectively. It was notable that most of the patients (19 patients, 86 %) were classified as having "unmeasurable" disease with a decreased level of iFLC<100 mg/L.

B Treatment details

The treatment details are summarized in **Table 2** and **Fig. 1**. The median initial, maximum, and ending doses of lenalidomide were 5.0 (range 2.5-5.0) mg, 10.0 (range 2.5-20) mg, and 7.5 (range 0.71-20) mg, respectively. The median initial and ending doses of dexamethasone were 40 (range 8-40) mg and 20 (range 0-40) mg, respectively. The median number of cycles needed to achieve hematological response (PR or better) and CR were 1 (range 1-7) and 2 (range 1-12), respectively. The median number of consolidation treatment cycles after achieving CR ($n=14$) was 4 (range 0-6).

C Outcomes

1 Hematological response

Treatment responses are summarized in **Table 2** and **Fig. 1**. Hematological response (PR or better) was observed in 16 patients (73 %). In detail, the numbers of patients who achieved CR, VGPR, PR, or NR were 14 (64 %), 0 (0 %), 2 (9 %), and 6 (27 %), respectively.

Table 3 Adverse events

Adverse event	Number of cases (n=22) Grade 1	2	3	4
Thrombocytopenia	0	0	1	0
Fatigue	2	2	3	0
Edema	0	0	1	0
Rash*	2	1	3	0
Dysgeusia	0	4	0	0
Anorexia	1	0	0	0
Muscle cramp	0	3	0	0
Peripheral sensory neuropathy	3	1	1	0
Respiratory infection	0	2	0	0
Urinary tract infection	0	1	0	0
Elevated creatinine level	1	2	0	0
Elevated AST and/or ALT level	1	0	1	0
Elevated alkaline phosphatase level	0	1	0	0

AST aspartate aminotransferase,
ALT alanine aminotransferase
*Including 1 case of Stevens-Johnson syndrome, Grade 3

2 Safety

Adverse events possibly related to treatment and their grades are summarized in **Table 3**. The numbers of patients with grade≥3 adverse events were

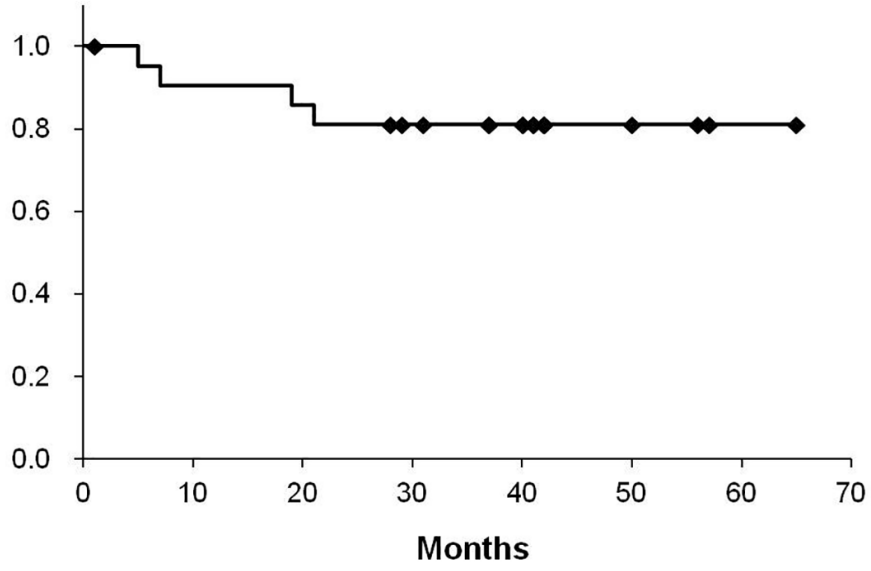

Fig. 2 Overall survival
The overall survival curve of 22 enrolled patients is shown (Kaplan–Meier method). Median overall survival has not yet been reached.

as follows : peripheral sensory neuropathy ($n=1$), edema ($n=1$), rash ($n=3$), thrombocytopenia ($n=1$), fatigue ($n=3$), and transaminase elevation ($n=1$). Rd therapy was discontinued due to toxicity in four patients (18 %, Pt01, 10, 17, and 22, **Fig. 1**). The detailed reasons for discontinuation in these four patients were as follows : Stevens–Johnson syndrome (grade 3) in Pt01, elevation of AST (grade 3), ALT (grade 3), and ALP (grade 2) in Pt10, deterioration of amyloid neuropathy (grade 3) in Pt17 (first discontinuation), fatigue (grade 3) and neuropathic pain (grade 3) in Pt17 (second discontinuation), and elevation of creatinine (grade 2) in Pt22. There were no cases of treatment-related death within 100 days after Rd initiation in this study (0 patients, 0 %).

3 Recurrence

Among the patients who achieved CR ($n=14$), hematological relapse (dropping out from the CR criterion) occurred in five patients (36 %) during the follow-up period (**Fig. 1**, **Table 2**). The median duration from achieving CR to relapse was 12 (range 2–35) months. The mean number of consolidation treatment cycles in the patients with relapse (2, range 0–3, $n=5$) tended to be lower than that in the patients without relapse (4.2, range 2–6, $n=9$) ($P=0.058$). Therefore, if tolerated, at least four cycles of consolidation treatment are recommended to prevent future relapse.

4 Re-treatment

All five patients with relapse received re-treatment with Rd (Pt 07, 10, 17, 18, and 21, **Fig. 1**). It is noteworthy that all except one of these patients achieved CR again ; the patient who did not achieve CR again (Pt07) was receiving ongoing Rd treatment without confirmed hematological response at the time of evaluation **(Fig. 1)**.

5 Survival

Four patients (Pt02, 08, 17, and 22, **Fig. 1**) died during the observation period. Three were due to disease progression (Pt02, 08, and 22) and the other was due to amyloidosis-unrelated disease progression (Pt22). The overall survival is shown in **Fig. 2**. The median overall survival has not yet been reached.

Ⅳ Discussion

Thalidomide and its analogs, lenalidomide and pomalidomide, are IMiDs that have been reported to have multiple actions with direct and/or indirect antitumor effects[18)19)]. Compared to thalidomide, two novel IMiDs, lenalidomide and pomalidomide, were reported to have potent anticancer activities and better tolerability profiles[18)19)]. Among these IMiDs, lenalidomide has been studied most extensively and is approved for treatment of patients with multiple myeloma (MM)[19)]. The dual actions of lenalidomide, i.e., direct tumoricidal activity and immunomodulatory effects, have been investigated and are now considered important underlying mechanisms of the fa-

vorable effect of this drug. The tumoricidal activities include disrupting stromal support of abnormal plasmacytes, upregulating tumor suppressor genes, inducing cell cycle arrest, and activating direct tumor cell apoptosis. The immunomodulatory effects include enhancing antigen-specific $CD8^+$ T cell cytolysis, increasing NK cell expression of death effector molecules, stimulating T cell proliferation and IFN-γ and IL-2 production, and reducing histone methylation and increasing histone acetylation at the p21 promoter[18)19)].

However, the number of previous reports describing the efficacy of lenalidomide against AL amyloidosis is very limited. There have been only four reports (three clinical trials and one observational study) to date regarding the Rd regimen in AL amyloidosis[9)-12)]. This is therefore only the second report describing the results of the Rd regimen in a retrospective study and is also the first report in an Asian cohort. **Table 4** presents a summary and comparison of these previous reports and the present study.

One of the notable features of this study was that the study design was highly consistent with the real-world clinical practice setting in two respects. First, patient backgrounds corresponded to those seen in clinical practice. Second, the treatment outcome evaluation criteria were updated. The patient backgrounds are often affected by the study design. Prospective clinical trials generally require some special inclusion and/or exclusion criteria and special treatment protocols to achieve a certain study purpose. For example, patients with "unmeasurable" disease with a decreased level of iFLC[9)] were excluded from previous studies because of the use of hematological response criteria, which required a "measurable" iFLC level to determine hematological response[15)]. Therefore, only those with higher titer iFLC were included in these previous studies. Therefore, this is the first report actively including patients with hematologically "unmeasurable" disease who are common targets of salvage therapy in current clinical settings but have been excluded from studies in the past **(Table 4)**. The method of treatment outcome evaluation is important. The old criteria used in the three previous studies[9)-11)] are not suitable to assess the treatment response in detail because the criteria lack a VGPR grade. Therefore, the results of hematological response in these studies could not be simply compared with current data. This study and a report from the UK[12)] are the only two reports to date evaluating the performance of the Rd regimen for AL amyloidosis using the updated hematological response criteria[17)]. Taken together, the patient backgrounds and manner of hematological response evaluation in this study are highly consistent with the current real-world practice setting compared to previous studies, and therefore provide important information for clinicians in current clinical practice.

Another notable feature of this study is that we achieved a better hematological response rate than previous reports **(Table 4)**. For example, the CR rate in this study was 64 % compared to 0 %–29 % in other reports, and the NR rate in this study was 27 % compared to 33 %–59 % in the other reports. The increased levels of iFLC in previous reports **(Table 4)** may have been responsible for their limited treatment outcomes because elevated dFLC (and therefore iFLC) is known to be a major correlate of disease severity[16)]. As described above, patients with "unmeasurable" disease with a decreased level of iFLC[9)] were excluded from previous studies, and so only those with higher titer iFLC were included.

A better outcome with regard to safety is also another feature of our study **(Table 4)**. In terms of salvage therapy, rapid response is not as important as in first-line therapy because the dFLC level would be already suppressed to some extent in most cases due to prior chemotherapy. Therefore, it is more important to continue the treatment safely until achieving CR without dropping out. Hence, the minimum-dose starting method may be a suitable treatment option. In the present study, lenalidomide was started at the minimum dose and then increased if tolerated to avoid the rapid emergence of severe adverse effects. In contrast, all of the previous studies began lenalidomide with the maximum dose and then reduced the dose if it was not well tolerated **(Table 4)**. Compared to the previous studies, the incidences of

Table 4 Summary and comparison of previous reports and this study

	Dispenzieri (Mayo), 2007 [9]	Sanchorawala (Boston), 2007 [10]	Palladini (Pavia), 2012 [11]	Mahmood (London), 2014 [12]	This study (Shinshu)
Type of study	Clinical trial	Clinical trial	Semi-clinical trial	Observational study	Observational study
Study design	Prospective	Prospective	Prospective	Retrospective	Retrospective
Patients with hematologically "unmeasurable"* disease	Excluded	ND	Excluded from evaluation	ND	Included
Median number of previous treatment regimens (range)	1 (0–3)	1 (0–5)	3 (2–5)	2 (1–6)	2 (1–4)
Type of previous treatment, number (%)					
Bortezomib and dexamethasone	ND	ND	24 (100.0)	58 (69)	21 (95.5)
Melphalan and dexamethasone	ND	ND	17 (70.8)	ND	11 (50.0)
High-dose melphalan with stem cell transplantation	6 (27.3)	19 (55.9)	7 (29.2)	13 (15.5)	3 (13.6)
Thalidomide based	ND	7 (20.6)	19 (79.2)	64 (76.1)	1 (4.5)
Median involved FLC, mg/L (range)	196 (22.6–7050)	ND	ND	109.5 (19.5–1480)	54.2 (12.2–516.0)
Median NT-proBNP, pg/mL (range)	1324.5 (109–42844)	ND	ND	1034 (110–79576)	876.9 (59.1–13529.0)
Organ involvement, number (%)					
Heart	14 (63.6)	13 (38.2)	16 (66.7)	42 (50)	13 (59.1)
Kidney	16 (72.7)	13 (38.2)	18 (75.0)	52 (61.9)	18 (81.8)
Standard starting dose of lenalidomide, mg	25	25	15	25	5
Lenalidomide dose adjusting manner	Reduced if untolerated	Reduced if untolerated	Reduced if untolerated	Reduced if untolerated	Increased if tolerated
Median number of total treatment cycles (range)	ND	6 (0–23)	4 (1–14)	6.5 (1–52)	6.5 (1–18)
Applied hematological response criteria	Old criteria [15]	Old criteria [15]	Old criteria [15]	New criteria [17]	New criteria [17]
Hematological response, number (%)	n = 22	n = 24	n = 22	n = 84	n = 22
CR	ND	7 (29.2)	0 (0.0)	17 (20)	14 (63.6)
PR or better (positive "hematologic response" on old criteria [15])	9 (40.9)	16 (66.7)	9 (40.9)	51 (61)	16 (72.7)
NR	13 (59.0)	8 (33.3)	13 (59.0)	33 (39)	6 (27.3)
Median number of cycles needed to achieve ≥ PR (range)	6.2 (ND)	6 (3–6)	< 2 (ND)	3 (1–19).	1 (1–7)
Number of patients who experienced grade ≥ 3 adverse event	19 (86.4)	ND	12 (50.0)	23 (27)	8 (36.4)
Number of patients who discontinued treatment due to toxicity	4 (18.2)	11 (32.4)	ND	ND	4 (18.2)
Treatment-related mortality (early deaths), number (%)	4 (18.2)	1 (2.9)	2 (8.3)	ND	0 (0.0)
Median survival, months	ND	ND	14	not reached	not reached

FLC free light chain, *NT-proBNP* N-terminal of the prohormone brain natriuretic peptide, *CR* complete response, *PR* partial response, *NR* no response, *ND* not described

*Patients WITHOUT serum monoclonal protein greater than or equal to 10 g/L (1.0 g/dL) by protein electrophoresis OR more than 200 mg monoclonal protein in the urine on 24-hour electrophoresis OR serum FLC greater than or equal to 100 mg/L along with an abnormal FLC κ/λ ratio were defined as hematologically "unmeasurable" disease [9].

severe adverse events, toxicity-related treatment discontinuation, and early death were lower in our study **(Table 4)**. Therefore, it is suggested that the safer profiles in our study may have been attributable to this careful treatment protocol. Starting with the maximum dose of lenalidomide (25 mg) may not be safe for some patients. Notably, although lenalidomide was initiated from the minimum dose in our study, the speed at which hematological response (PR or better) was achieved was equivalent to or faster than that in previous reports **(Table 4)**.

In conclusion, our study provided important insight for clinicians treating AL patients in the real world because patient backgrounds and updated evaluation criteria were highly consistent with current clinical practice settings. The Rd regimen used in this study was sufficiently safe and effective for patients with relapsed and/or refractory AL amyloidosis. The decreased level of iFLC and safer treatment protocol were thought to be responsible for these outcomes.

Acknowledgments

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Compliance with Ethical Standards

Ethics

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent for receiving Rd treatment was obtained from all enrolled patients. This study protocol was approved by the Ethics Committee of Shinshu University School of Medicine (No. 3988).

Conflict of Interest

The authors declare that they have no conflicts of interest.

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