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【 ORIGINAL ARTICLE 】

Combined Therapy with Ixazomib, Lenalidomide, and Dexamethasone for Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes Syndrome

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Abstract:

Objective Immunomodulatory drugs and proteasome inhibitors are therapeutic options for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. This study aimed to evaluate the efficacy and safety of the combination of ixazomib, lenalidomide, and dexamethasone (IRd) for POEMS syndrome.

Methods Six consecutive patients with POEMS syndrome who were treated with the IRd regimen at Chiba University Hospital between April 2018 and August 2021 were included. Serum M-protein and serum vascular endothelial growth factor (sVEGF) levels, overall neuropathy limitation scales (ONLS), clinical symptoms, and adverse events were assessed.

Results Of the six patients, five had received prior treatments. Patients received a median of 5 cycles (range, 3-28 cycles) of IRd. Following treatment, serum M-protein disappeared in two patients, sVEGF levels returned to normal in two patients, two patients showed a reduction in the ONLS of 1, and clinical symptoms improved in four patients. The median level of sVEGF decreased from 2,395 pg/mL (range, 802-6,120 pg/mL) to 1,428 pg/mL (range, 183-3,680 pg/mL) in three months. Adverse events, including rash, neutropenia, sensory peripheral neuropathy, and nausea, were observed in three patients, which necessitated dose reduction or discontinuation of treatment.

Conclusion IRd can be a therapeutic option for POEMS syndrome, albeit with careful monitoring of adverse events.

Key words: POEMS syndrome, proteasome inhibitors, immunomodulatory drugs, ixazomib, lenalidomide, vascular endothelial growth factor (VEGF)

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare plasma cell proliferative disorder characterized by multiple organ involvement (1). Although the pathogenesis of POEMS syndrome remains unclear, plasma cell dyscrasia and overproduction of vascular endothelial growth factor (VEGF) are believed to play an important role in its patho-

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physiology (1, 2). VEGF stimulates vascular permeability and angiogenesis and may be responsible for some symptoms, such as edema/effusion, skin hemangioma, and hepatosplenomegaly (2).

Based on their association with plasma cell dyscrasia, patients with POEMS syndrome have been treated with therapeutic interventions for multiple myeloma, such as high-dose chemotherapy with autologous stem cell transplantation (ASCT) (3-5), alkylating agents (6), immunomodulatory drugs (IMiDs) (7-10), and proteasome inhibitors (PIs) (11-14). These treatments considerably improved the prognosis of patients with POEMS syndrome (15, 16). Thus, new therapeutic agents used for treating multiple myeloma may also be applied to POEMS syndrome, and patients with POEMS syndrome are expected to achieve improved outcomes.

Combination therapies of PIs, IMiDs, and corticosteroids are effective regimens for multiple myeloma (17). Ixazomib is an oral PI used for treating multiple myeloma, and its combination with lenalidomide, an immunomodulatory drug, and dexamethasone, a glucocorticoid, is a therapeutic option for patients with multiple myeloma (18, 19). We therefore speculated that ixazomib, lenalidomide, and dexamethasone (IRd) might also be effective in treating POEMS syndrome. The present study investigated the efficacy and safety of IRd in patients with POEMS syndrome.

Materials and Methods

Patients

This retrospective observational study included six consecutive patients with POEMS syndrome who were treated with IRd at Chiba University Hospital between April 2018 and August 2021. The diagnosis of POEMS syndrome was established based on published diagnostic criteria (20). The IRd regimen comprised a 28-day cycle with oral ixazomib on days 1, 8, and 15; oral lenalidomide on days 1-21; and oral dexamethasone once a week.

The ethics committee of Chiba University Hospital approved off-label use of IRd for POEMS syndrome, and the ethics committee of Chiba University School of Medicine approved this study. All patients provided their written informed consent for the publication of their anonymous data.

Assessments

All patients underwent physical and neurological examinations, blood tests, whole-body computed tomography (CT), and nerve conduction studies as per routine practice. The following variables were assessed: the age, sex, duration of disease, history of previous treatments, clinical symptoms related to POEMS syndrome, overall neuropathy limitations scale (ONLS), and M-protein and VEGF levels. M-protein were assessed in serum using immunofixation. VEGF levels were measured in serum, as the reduction of serum VEGF (sVEGF) levels after treatment significantly correlates with the relapse-free survival and clinical improvement in patients with POEMS syndrome (21). sVEGF levels were measured using an enzyme-linked immunosorbent assay (normal <1,000 pg/mL; Special Reference Laboratory, Tokyo, Japan) (21).

Treatment response

Hematologic, VEGF, neurologic, and other responses were evaluated. The hematologic response included complete response (CR_H), defined as a negative result in serum immunofixation, and no-CR_H (9). The VEGF response included complete response (CR_V), defined as normalization of sVEGF levels (<1,000 pg/mL); partial response (PR_V), defined as decrease in sVEGF levels by at least 50%; and stable disease (SD_V), defined as not meeting the criteria for either CR_V or PR_V (9). Neurological response (R_N) was defined as a ≥1-point reduction in the ONLS score (9). Other responses included organomegaly, extravascular volume overload, and skin change response, which were defined as the objective improvement in each symptom based on physical examinations and CT findings. Patients who did not meet the criteria for a measurable parameter were excluded from the evaluation of that parameter.

Adverse events

Adverse events were assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Results

Characteristics of patients

Table 1 shows the characteristics of patients who received IRd. Of the 6 patients, 3 were men, with a median age of 56 (range, 32-75) years old, and the median time from the diagnosis was 56 (range, 2-192) months. POEMS syndrome was newly diagnosed for one patient (case 5), and five patients had been treated previously. Of the five who had been treated previously, the syndrome relapsed in one (case 2) after lenalidomide and dexamethasone (Rd) treatment and in four (cases 1, 3, 4, and 6) after ASCT. Case 6 had received bortezomib and dexamethasone for relapse, and the sVEGF levels normalized before IRd administration. All patients had serum M-protein. All patients had demyelinating polyneuropathy, confirmed using nerve conduction studies, while five patients presented with ONLS scores of ≥1.

Table 2 shows responses to the previous treatment with thalidomide, lenalidomide, and bortezomib. Case 1 was refractory to thalidomide and bortezomib. Although case 2 was refractory to thalidmide, he responded to lenalidomide. Case 3 was refractory to both thalidomide and lenalidomide; however, she partially responded to bortezomib. Case 4 was refractory to both lenalidomide and bortezomib. Case 6 responded well to bortezomib.

Table 1. Baseline Characteristics of Patients.

Case No.	Sex	Age	Time from diagnosis (months)	History of treatment	M-protein	sVEGF level (pg/mL)	ONLS (Arm/Leg)	Sclerotic bone lesions	Organomegaly	Extravascular volume overload	Skin changes
1	M	61	178	ASCT, Td, Bd, VCd, 2nd ASCT	IgG-λ	3,170	2/2	+	-	-	+
2	M	51	192	Td, Rd	IgA-λ	1,680	1/1	+	+	-	+
3	F	61	76	Td, Rd, Bd, ASCT	IgG-λ	1,820	2/2	+	+	-	+
4	M	32	9	Bd, VRd, ASCT	IgA-λ	2,970	0/0†	+	+	+	-
5	F	75	2	None	IgA-λ	6,120	0/2	+	+	+	+
6	F	43	36	Bd, ASCT, 2nd Bd	IgG-λ	802	0/2	+	+	+	+

†Demyelinating polyneuropathy confirmed using nerve conduction studies. ASCT: autologous stem cell transplantation, Td: thalidomide and dexamethasone, Rd: lenalidomide and dexamethasone, Bd: bortezomib and dexamethasone, VCd: bortezomib, cyclophosphamide, and dexamethasone, VRd: bortezomib, lenalidomide, and dexamethasone, ONLS: overall neuropathy limitations scale, sVEGF: serum vascular endothelial growth factor

Table 2. Response to the Previous Treatment with Thalidomide, Lenalidomide, and Bortezomib.

	Thalidomide and dexamethasone		Lenalidomide and dexamethasone		Bortezomib and dexamethasone	
Case No.	Hematologic response	VEGF response	Hematologic response	VEGF response	Hematologic response	VEGF response
1	No-CR	SD	-	-	No-CR (No-CR†)	SD (PR†)
2	No-CR	SD	No-CR	CR	-	-
3	No-CR	SD	No-CR	SD	No-CR	PR
4	-	-	No-CR‡	SD‡	No-CR	SD
5	-	-	-	-	-	-
6	-	-	-	-	CR	CR

†Addition of cyclophosphamide. ‡Addition of lenalidomide to bortezomib and dexamethasone. CR: complete response, PR: partial response, SD: stable disease, VEGF: vascular endothelial growth factor

Treatment response

Table 3 summarizes the responses to IRd. Patients received a median of 5 cycles (range, 3-28 cycles) of IRd. The initial doses of IRd were as follows: 4 mg ixazomib, 5 mg lenalidomide, and 20 mg dexamethasone for 3 patients (cases 1, 3, and 5); 4 mg ixazomib, 15 mg lenalidomide, and 20 mg dexamethasone for 1 patient (case 2); 4 mg ixazomib, 25 mg lenalidomide, and 20 mg dexamethasone for 2 patients (cases 4 and 6).

Two patients (cases 5 and 6) achieved CR_H, and the remaining four had no-CR_H. Two cases of CR_H were observed at 3 and 10 months. Cases 2, 5, and 6 showed a rapid decrease in sVEGF levels after treatment, whereas cases 1, 3, and 4 showed an inadequate VEGF response (Figure). The median sVEGF levels decreased from 2,395 pg/mL (range, 802-6,120 pg/mL) to 1,428 pg/mL (range, 183-3,680 pg/mL) after 3 months. Of the five patients with elevated sVEGF levels, two (cases 2 and 5) achieved CR_V, and three (cases 1, 3, and 4) had SD_V at three months. Two patients (cases 2 and 5) achieved R_N, and both had 1-point reductions in their ONLS score. Three patients (cases 1, 4, and 5) underwent nerve conduction studies before and after IRd. Cases 1 and 5 showed an improvement in median nerve motor conduction velocities (case 1: from 43 m/s to 50 m/s at 4 months, case 5: from 35 m/s to 41 m/s at 3 months). Four patients showed other responses, including three (cases 2, 5, and 6) with an organomegaly response, three (cases 4, 5, and 6) with an extravascular volume overload response, and two (cases 5 and 6) with a skin change response. None of the patients died during follow-up. Cases 1, 3, and 4 showed a poor response to IRd, and subsequently, case 1 received ASCT a third time, and cases 3 and 4 received daratumumab, lenalidomide, and dexamethasone. These were refractory cases, as each had a poor response to the previous thalidomide-, lenalidomide-, and/or bortezomib-based regimens (Table 2).

Adverse events

Five patients experienced adverse events (Table 4). Case 2 developed a grade 3 rash on day 4 of the first cycle and suspended IRd. After the rash disappeared completely, IRd was resumed at a reduced dose (I, 3 mg; R, 15 mg; d, 20 mg). Case 5 developed a grade 2 rash during the third cycle. The rash resolved after the patient discontinued ixazomib, so she instead received Rd for six cycles, resulting in an increase in

Table 3. Response to IRd.

Case No.	No. of IRd cycles	Dose of I, R, d (mg)	Hematological response		VEGF response		Neurological response		Organomegaly response		Extravascular volume overload response		Skin change response	
			At 3 months	At last visit	At 3 months	At last visit	At 3 months	At last visit	At 3 months	At last visit	At 3 months	At last visit	At 3 months	At last visit
1	4	4, 5, 20	No-CR	No-CR	SD	SD	No	No	-	-	-	-	No	No
2	21	4 (3†), 15, 20	No-CR	No-CR	CR	CR	No	Yes	No	Yes	-	-	No	No
3	3	4, 5, 20	No-CR	No-CR	SD	SD	No	No	No	No	-	-	No	No
4	3	4, 25, 20	No-CR	No-CR	SD	SD	-	-	No	No	Yes	Yes	-	-
5	28	4 (2.3†), 5 (10-15†), 20	No-CR	CR	CR	PR	Yes	Yes	No	Yes	Yes	Yes	No	Yes
6	6	4, 25, 20	CR	CR	-	-	No	No	Yes	Yes	Yes	Yes	Yes	Yes

†Adjusted dose after adverse events. IRd: ixazomib, lenalidomide, and dexamethasone, CR: complete response, PR: partial response, SD: stable disease, VEGF: vascular endothelial growth factor

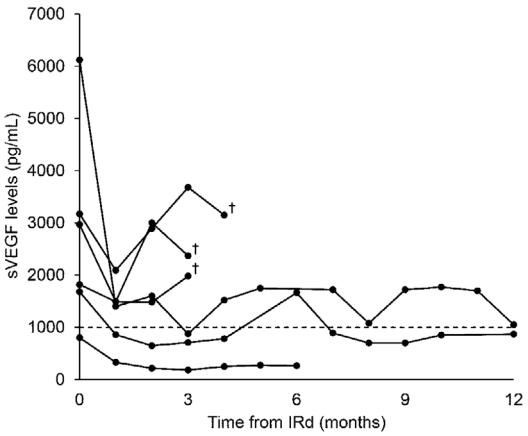

Figure. Serial changes in the levels of serum vascular endothelial growth factor. Dotted lines indicate the upper limit of the normal range. †Discontinuation of IRd. IRd: ixazomib, lenalidomide, and dexamethasone, sVEGF: serum vascular endothelial growth factor

sVEGF levels from 875 to 1,770 pg/mL. She resumed IRd at a reduced dose (I, 2.3 mg; R, 15 mg; d, 20 mg), following which sVEGF levels decreased again. Case 5 also developed grade 2 neutropenia and sensory peripheral neuropathy that required a dose reduction of lenalidomide from 15 to 10 mg. Case 4 experienced nausea, resulting in IRd discontinuation.

Discussion

To our knowledge, this is the first case series of IRd in patients with POEMS syndrome. IRd was effective in three of six patients and contributed to the disappearance of serum M-protein, decreased sVEGF levels, and clinical improvement. However, this was accompanied by alarming adverse events such as rash, nausea, neutropenia, and sensory peripheral neuropathy, which were handled by reducing the treatment intensity or discontinuing treatment. Our results suggest that IRd may be a therapeutic option for POEMS syndrome.

PIs and IMiDs are currently used to treat POEMS syndrome (16). The efficacy of bortezomib, an injectable PI, for POEMS syndrome has been reported in case series/reports (11-14). The IMiDs, thalidomide and lenalidomide, have been administered to patients with POEMS syndrome, and their efficacies have been demonstrated in several clinical trials (7-10). Although each agent is a promising therapy for POEMS syndrome, the efficacy of their combination has not been investigated. The present study is the first to show the potential efficacy of IRd, a combination of PIs and IMiDs, in POEMS syndrome. Furthermore, IRd is suitable for long-term treatment, as all of the agents are administered as oral drugs.

Ixazomib selectively binds to the β5 site of the S20 proteasome, inhibits its chymotrypsin-like activation, and induces the accumulation of ubiquitinated proteins (22). This induces apoptosis in the tumor cells. Cereblon is the primary target of lenalidomide. The binding of lenalidomide to cereblon causes ubiquitination of IKZF1 and IKZF3, promoting their degradation and resulting in anti-tumor effects (23, 24). The mechanisms of action of ixazomib and lenalidomide differ, which is useful for treating POEMS syndrome. Therefore, IRd can be effective for a broad range of patients. In addition, ixazomib has been shown to exert synergistic effects when used with lenalidomide in preclinical studies (25). The TOURMALINE-MM1 study, a phase 3 trial of ixazomib-Rd versus placebo-Rd in patients with relapsed/refractory multiple myeloma, showed that the addition of ixazomibe to Rd prolonged the progression-free survival (18). We previously conducted a clinical trial of Rd in five patients with POEMS syndrome (10); however, we were unable to compare the results of the present study with those of our previous clinical trial because the patient backgrounds differed between the two studies.

Table 4. Adverse Events.

Case No.	Grade 1	Grade 2	Grade 3
1	ALT elevation, AST elevation	-	-
2	-	-	Rash†
3	-	-	-
4	-	Nausea†	-
5	-	Rash†, sensory peripheral neuropathy†	Neutropenia†
6	Somnolence	-	-

†Causes of dose reduction or withdrawal. ALT: alanine aminotransferase, AST: aspartate aminotransferase

According to the TOURMALINE-MM1 study, the common adverse events related to IRd included thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, constipation, rash, peripheral neuropathy, peripheral edema, and back pain (18, 26). These adverse events were generally mild and manageable, although sometimes they had to be managed with supportive care and dose reductions (26). In the present study, neutropenia, nausea, rash, and peripheral neuropathy affected the treatment course. Thus, awareness regarding potential toxicities is critical for handling them appropriately.

Several limitations associated with the present study warrant mention. This was a retrospective study conducted on a small number of patients over a short period. Of the six cases, three (cases 1, 3, and 4) received only three or four cycles of treatment. The reason underlying the poor response to IRd may be the short duration of treatment, or the patients may have been refractory to the previous IMiDs and/or PIs and consequently were refractory to IRd as well (Table 2). In contrast, the patients who had had a good response to IRd, except for the newly diagnosed patient (case 5), were sensitive to the previous lenalidomide (case 2) and bortezomib (case 6). The doses of ixazomib and lenalidomide differed among cases, which was an important issue; therefore, the use of IRd in treating POEMS syndrome bears further investigation. Prospective investigations should be conducted in a larger number of patients undergoing long-term treatment to confirm our results.

In conclusion, our results indicated that IRd was effective in some patients with POEMS syndrome. However, the treatment can be accompanied by hematological, gastrointestinal, neurological, and dermatological toxicities. An open-label phase 2 clinical trial is underway in the USA (ClinicalTrials.gov number, NCT02921893), and the efficacy and safety of IRd for POEMS syndrome are expected to be validated.

The ethics committee of Chiba University Hospital approved off-label use of ixazomib, lenalidomide, and dexamethasone for POEMS syndrome. The ethics committee of the Chiba University School of Medicine approved this study.

All patients provided their written informed consent.

The authors state that they have no Conflict of Interest (COI).

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