Lenalidomide Treatment for Thalidomide-refractory POEMS Syndrome: A Prospective Single-arm Clinical Trial

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Abstract:
Objective A randomized controlled trial has shown the efficacy of thalidomide against Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome; however, there are still refractory patients. We studied the effects of lenalidomide, a derivative of thalidomide, on patients refractory to thalidomide.

Methods This prospective single-arm trial evaluated the safety and efficacy of lenalidomide plus dexamethasone in refractory or recurrent patients with POEMS syndrome. The regimen was administered as six 28-day cycles with lenalidomide on days 1-21 (15 mg in cycle 1, and 25 mg in cycle 2-6) plus dexamethasone once a week (20 mg). The primary endpoints were the rate of reduction in the serum vascular endothelial growth factor (VEGF) level at 24 weeks and the incidence of adverse events. This trial was registered with ClinicalTrial.gov, NCT02193698.

Results Between July 2014 and December 2015, five men were enrolled. All patients had been refractory to thalidomide plus dexamethasone for more than 24 weeks. The mean rate of reduction in the serum VEGF level at 24 weeks was 59.6%±8.3% (p=0.0003). The mean serum VEGF level decreased from 2,466±771 pg/mL to 974±340 pg/mL. No serious adverse events were observed, and all patients completed six cycles treatment.

Discussion Lenalidomide is a therapeutic option for thalidomide-refractory patients with POEMS syndrome.

Key words: POEMS syndrome, clinical trial, lenalidomide, thalidomide, VEGF

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare devastating disorder characterized by demyelinating polyneuropathy (1). Plasma cell dyscrasia and the overproduction of vascular endothelial growth factor (VEGF) play a fundamental role in the pathophysiology of this disease (1, 2), and the VEGF level correlates well with the clinical improvement and prognosis (3, 4).

Recently, several myeloma treatments have been attempted in patients with POEMS syndrome, showing an improved prognosis (2). Thalidomide is the only drug whose safety and efficacy in POEMS syndrome has been demonstrated by a randomized placebo-controlled trial, and it has since become the first-line treatment (5). However, some patients still cannot achieve remission even with thalidomide (5).

Lenalidomide is a derivative of thalidomide, whose safety and efficacy in patients with newly diagnosed or recurrent POEMS syndrome have been reported (6-11). This study...
was a prospective single-arm trial performed to evaluate the safety and efficacy of lenalidomide in patients with refractory or recurrent POEMS syndrome.

**Materials and Methods**

**Study design and patients**

This prospective single-arm trial was conducted at Chiba University Hospital, Chiba, Japan. It comprised a 24-week treatment period followed by a 4-week observation period. Patients were recruited from May 2014 to April 2016. They received six 28-day cycles of lenalidomide plus dexamethasone regimen, which is based on the regimen used for the treatment of myeloma (12). This regimen comprised oral lenalidomide daily on days 1-21 (15 mg in cycle 1, and 25 mg in cycle 2-6) plus 20 mg oral dexamethasone on days 2, 9, 16, and 23. This trial was registered with ClinicalTrials.gov (NCT02193698).

Adults (≥ 20 years old) with probable or definite POEMS syndrome according to the published diagnostic criteria (13) were eligible if they had recurrent or refractory disease. Recurrent patients were defined as those whose disease had progressed after temporary remission. Refractory patients were defined as those who had not been able to achieve remission despite a history of 24-week treatment. Patients were ineligible if they had received bortezomib, lenalidomide, or melphalan within 4 weeks; corticosteroid (≥ 10 mg/day) within 2 weeks; or bevacizumab within 12 weeks at enrollment. Patients who had an unstable disease status or severe complications (cardiac/renal/hepatic failure, hemorrhagic ulcer, intestinal obstruction, severe diabetes mellitus, or other malignancies) were also excluded.

The review board of Chiba University Hospital approved the study protocol. All patients provided their written informed consent.

**Assessments and study endpoints**

Patients were assessed at study entry, on day 1 of each cycle, and on the last day of the treatment period. Clinical assessments, blood and urine tests, chest radiography, and electrocardiograms were performed at study entry, at each visit, and on the last day of the treatment period. Whole-body computed tomography (CT) was performed on day 1 of cycles 1 and 4 and on the last day of the treatment period. Nerve conduction studies and respiratory function tests were performed on day 1 of cycle 1 and the last day of the treatment period. Adverse events were assessed at each visit, the last day of the treatment period, and the last day of the observation period.

The primary endpoints were the rate of reduction in the serum VEGF level at 24 weeks (efficacy) and the incidence of adverse events (safety). The rate of reduction in the serum VEGF level was defined as follows: [(VEGF level at baseline - VEGF level at 24 weeks) / VEGF level at baseline]. The adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

The secondary endpoints were the serum VEGF level, normalization of the serum VEGF level (<1,000 pg/mL (4)), complete or partial remission rate, M-protein (immunofixation electrophoresis), motor function (manual muscle testing, grip strength, and overall neuropathy limitation scale), parameters of nerve conduction studies (motor conduction velocity, compound muscle action potential amplitude, F-wave latency, sensory conduction velocity, and sensory nerve action potential amplitude), pleural effusion, vital capacity, bodyweight, and completion rate of treatment. Partial remission was defined as the normalization of the serum VEGF level only, and complete remission was defined as the normalization of the serum VEGF level and the disappearance of M-protein. These definitions were based on the findings of a previous report on the relationship between the VEGF level and clinical improvement (4), and the pathophysiology of POEMS syndrome. The achievement of normalized VEGF levels is significantly associated with an extended relapse-free survival (4). In addition, changes in M-protein from positive to negative can suggest substantial suppression of monoclonal plasma cell proliferation, which plays a key role in the pathophysiology of POEMS syndrome.

**Statistical analyses**

The study was designed to enroll five recurrent or refractory patients. A mean rate of reduction of 0.10 was unacceptable and was used as a historical control. Assuming a mean rate of reduction of 0.45±0.25 with lenalidomide and a threshold value of 0.10, 4 patients provided a power of > 80% using a 1-sided 1-sample t-test at a 5% level of significance. Considering possible protocol violations and dropouts, the target sample size was set at five patients.

Analyses of primary and secondary endpoints were performed with the full analysis set. For baseline variables, summary statistics were calculated using the frequency and proportion for the categorical variables and the mean and standard deviation for the continuous variables. For primary efficacy, the mean rate of reduction in the serum VEGF level at 24 weeks was compared to that of the historical control by a 1-sided 1-sample t-test (H0: mean rate of reduction ≤10%, H1: mean rate of reduction >10%). The 2-sided 90% confidence interval (CI) of the mean rate of reduction was also calculated. For the secondary analysis, summary statistics were provided. These statistical analyses were pre-specified in the study protocol. We performed a paired t-test for the secondary endpoints at 0 and 24 weeks to investigate the clinical improvement.

All statistical analyses were performed using the software programs SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and JMP pro 13.0.0 (SAS Institute Inc., Cary, NC, USA).
Patients

Between July 2014 and December 2015, we enrolled 5 men (median age, 52 years old). Table 1 shows the baseline characteristics of the patients. All patients had been refractory to treatment with thalidomide plus dexamethasone for more than 24 weeks.

Efficacy

Figure A shows the sequential changes in the rate of reduction in the serum VEGF level, which is the primary efficacy endpoint. The mean rate of reduction in the serum VEGF level at 24 weeks was 59.6%±8.3% (90% CI, 50.8%–68.4%; p=0.0003) (H: mean rate of reduction, ±10%). The mean serum VEGF level decreased from 2,466±771 pg/mL to 974±340 pg/mL (p=0.0055) (Figure B). Table 2 shows the secondary endpoints at each visit. With the lenalidomide plus dexamethasone regimen for 24 weeks, partial and complete remission was achieved in 80% and 20% of the patients, respectively. The other clinical and neurophysiological parameters did not show any significant improvement; however, most parameters improved.

Safety

All patients experienced adverse events. The IgG level decreased in two patients (Grade 1 and 2), the urinary sugar level increased in two patients (Grade 1), bronchial infection was detected in one patient (Grade 1), and constipation was reported by one patient (Grade 2). Sinus bradycardia, which is frequently caused by thalidomide (5), was not observed. No serious adverse events were reported, and all patients completed treatment for six cycles.

Discussion

This prospective single-arm trial first showed that lenalidomide plus dexamethasone contributed to the reduction in the serum VEGF level and achievement of partial/complete remission, defined as normalization of VEGF level and/or disappearance of M-protein in patients with POEMS syndrome who were refractory to thalidomide plus dexamethasone for more than 24 weeks.

Table 1. Baseline Characteristics of Patients with POEMS Syndrome.

| Characteristics | n=5 |
|-----------------|-----|
| Age, years      | 52 (45–58) |
| Male sex        | 5 (100) |
| Disease duration, months | 47 (24–116) |
| ECOG Performance status | 1 (1–3) |
| Prior-line treatments, 1−2−3 lines | 2 (40)−1 (20)−2 (40) |
| Thalidomide     | 5 (100) |
| Corticosteroid  | 3 (60) |
| Autologous stem cell transplantation | 2 (40) |
| Radiation       | 0 (0) |
| Complications   | 5 (100) |
| Constipation    | 4 (80) |
| Diabetes mellitus | 3 (60) |
| Hypertension    | 2 (40) |
| Hyperlipidemia  | 2 (40) |
| Hyperuricemia   | 2 (40) |
| Hypertriglyceridemia | 1 (20) |
| Gallbladder polyp | 1 (20) |
| Maxillary cyst  | 1 (20) |
| Serum VEGF level, pg/mL | 2,466 (771) |
| M-protein       | 5 (100) |

Data are represented as the median (range), mean (SD), or number (%).

POEMS: polynuropathy, organomegaly, endocrinopathy, M-protein, and skin changes, ECOG: Eastern Cooperative Oncology Group, VEGF: vascular endothelial growth factor.

Figure. Sequential changes in the serum VEGF level. (A) Sequential changes in the rate of reduction in the serum VEGF level. The primary endpoint was the mean rate of reduction in the serum VEGF level at 24 weeks (59.6%±8.3%; 90% CI 50.8–68.4; p=0.0003). (B) Sequential changes in the serum VEGF level. CI: confidence interval, SD: standard deviation, VEGF: vascular endothelial growth factor.
should be performed to identify the strengths and weaknesses of the different options, determine the clinical profiles of the suitable patients for each treatment, and establish an efficient therapeutic strategy.

From this perspective, thalidomide is preferred to lenalidomide at this point because the former’s efficacy and safety have been demonstrated in a controlled trial (5). However, lenalidomide is a viable option for treating patients refractory to thalidomide, given its broader immunomodulatory and stronger anti-tumor effects than thalidomide (17). The adverse effects of each drug should be considered. Thalidomide has a major advantage over lenalidomide in terms of its weaker myelosuppression. For autologous transplantation candidates in particular, the poor mobilization of autologous stem cells caused by lenalidomide can be a critical issue. The treatment duration of lenalidomide should therefore be limited to within four cycles for young patients scheduled to undergo autologous transplantation in the future (18). Lenalidomide is a suitable option for patients who must discontinue thalidomide therapy due to sensory neuropathy or cardiotoxicity because of its lower neurotoxic (19) and cardiotoxic potential than thalidomide.

amethasone for more than 24 weeks. We also showed the safety of lenalidomide in those patients.

Several studies have shown that therapeutic modalities for myeloma, such as auto-transplantation, immunomodulatory drugs, and proteasome inhibitors, are also effective against POEMS syndrome (2). Among these, thalidomide is the only agent whose efficacy and safety have been demonstrated by a randomized placebo-controlled study (5). The efficacy and safety of lenalidomide in newly diagnosed or relapsed patients with POEMS syndrome have also been explored in a large case series (8, 9) and in two one-arm clinical trials (10, 11). Several new agents for myeloma, such as daratumumab, may be effective in POEMS syndrome as well (14).

As the peak age of onset of POEMS syndrome is lower than that of myeloma (15, 16), the disease must be controlled for decades. For each patient with POEMS syndrome, we must select the most appropriate treatment from among the several different therapeutic options available for myeloma treatment. Therefore, prospective clinical trials should be performed to identify the strengths and weaknesses of the different options, determine the clinical profiles of the suitable patients for each treatment, and establish an efficient therapeutic strategy.

Table 2. Secondary Endpoints at Each Visit.

|                  | A. At 0 weeks (N=5) | B. At 4 weeks (N=5) | C. At 8 weeks (N=5) | D. At 12 weeks (N=5) | E. At 16 weeks (N=5) | F. At 20 weeks (N=5) | G. At 24 weeks (N=5) | p value (A vs G) |
|------------------|---------------------|---------------------|---------------------|----------------------|---------------------|--------------------|--------------------|-----------------|
| Serum VEGF levels, pg/mL | 2.466 (771) | 1.560 (188) | 1.206 (141) | 1.194 (179) | 1.039 (154) | 1.180 (430) | 0.0055 |
| Normalization of serum VEGF level | 0 (0) | 0 (0) | 0 (0) | 1 (20) | 2 (40) | 2 (40) | 4 (80) |
| Absence of M-protein | 0 (0) | 0 (0) | 0 (0) | 1 (20) | 2 (40) | 2 (40) | 4 (80) |
| Hematologic response | Complete remission | 0 (0) | 0 (0) | 0 (0) | 1 (20) | 1 (20) | 1 (20) |
| Partial remission | 0 (0) | 0 (0) | 0 (0) | 1 (20) | 2 (40) | 2 (40) | 4 (80) |
| Motor function | Sum score of manual muscle testing | 66.80 (4.60) | 66.80 (4.60) | 67.20 (3.90) | 67.40 (3.58) | 66.70 (3.29) | 0.37 |
| Grip strength (average of both sides), kg (11.32) | 26.95 | 27.55 | 28.00 | 29.25 | 28.50 | 29.00 | 25.75 | 0.054 |
| Overall neuropathy limitation scale | Total score | 2.60 (2.30) | 2.60 (2.30) | 2.60 (1.82) | 2.60 (1.82) | 2.60 (1.82) | 2.60 (1.82) | 1 |
| Arm score | 1.40 (1.14) | 1.40 (1.14) | 1.60 (0.89) | 1.60 (0.89) | 1.60 (0.89) | 1.60 (0.89) | 1.60 (0.89) | 0.37 |
| Leg score | 1.20 (1.30) | 1.20 (1.30) | 1.00 (1.00) | 1.00 (1.00) | 1.00 (1.00) | 1.00 (1.00) | 1.00 (1.00) | 0.37 |
| Median nerve conduction parameters | CMAP amplitude, mV | 5.74 (2.24) | NA | NA | NA | NA | 7.24 (1.86) | 0.12 |
| Motor conduction velocity, m/s | 43.60 (5.98) | NA | NA | NA | NA | 44.20 (5.63) | 0.65 |
| F-wave latency, ms | 35.33 (6.56) | NA | NA | NA | NA | 35.56 (5.56) | 0.33 |
| SNAP amplitude, μV | 6.00 (2.35) | NA | NA | NA | NA | 8.20 (5.26) | 0.34 |
| Sensory conduction velocity, m/s | 45.60 (6.58) | NA | NA | NA | NA | 45.00 (6.71) | 0.80 |
| Sural nerve conduction parameters | SNAP amplitude, μV | 2.00# | NA | NA | NA | 2.00 (0.00)# | - |
| Sensory conduction velocity, m/s | 49.00# | NA | NA | NA | NA | 41.00 (1.41)# | - |
| Presence of pleural effusion | 2 (40) | NA | 1 (20) | NA | NA | 1 (20) | |
| Vital capacity, L | 3.19 (1.12) | NA | NA | NA | NA | 3.16 (1.12) | 0.31 |
| Body weight, Kg | 69.00 | 68.44 | 68.32 | 68.52 | 69.28 | 69.22 | 69.62 | 0.51 |

Data are mean (SD) or number (%). *N=4 (one missing data). SNAP was evoked in one patient. SNAP was evoked in two patients. NA: Not applicable, SD: standard deviation, VEGF: vascular endothelial growth factor, CMAP: compound muscle action potential, SNAP: sensory nerve action potential.

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This study is associated with several limitations. First, this was a single-arm trial enrolling a small number of participants. Our results should be validated in a larger number of patients. Second, this trial failed to show evident clinical improvement, although it successfully demonstrated the reduction and normalization of the VEGF level after treatment. A previous study showed that a reduction in VEGF is followed by clinical and laboratory improvements after six months, and normalization of the VEGF level is associated with a longer relapse-free survival (4). Therefore, the VEGF reduction achieved with lenalidomide in the present study may imply clinical improvement later.

In summary, lenalidomide plus dexamethasone is safe and effective in thalidomide-refractory patients with POEMS syndrome. POEMS syndrome is so rare and severe that it is challenging to conduct clinical trials and quality observational studies. However, continuous efforts to conduct prospective clinical trials that prioritize each therapeutic option are essential for the establishment of therapeutic strategies and ensuring a better prognosis of the disease.

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

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Contributors: TS, SM, KK, and SK designed the study. YI, YS, KS, HA, YS, AT, and KN collected data. TS, KN, and YS performed statistical analyses. TS, SM, and SK interpreted the results. TS, SM, KN, and SK drafted the manuscript.

Trial registration: ClinicalTrials.gov (NCT02193698).

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