Japanese POEMS syndrome with Thalidomide (J-POST) Trial: study protocol for a phase II/III multicentre, randomised, double-blind, placebo-controlled trial.

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Japanese POEMS syndrome with Thalidomide (J-POST) Trial: study protocol for a phase II/III multicentre, randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction: Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS) syndrome is a fatal systemic disorder associated with plasma cell dyscrasia and the overproduction of the vascular endothelial growth factor (VEGF). Recently, the prognosis of POEMS was substantially improved by introduction of therapeutic intervention for myeloma. However, no randomised clinical trial has been performed because of the rarity and severity of the disease.

Methods and analysis: The Japanese POEMS syndrome with Thalidomide (J-POST) Trial is a phase II/III multicentre, double-blinded, randomised, controlled trial that aims to evaluate the efficacy and safety of a 24-week treatment with thalidomide in POEMS syndrome, with an additional 48-week open-label safety study. Adults with POEMS syndrome who have no indication for transplantation are assessed for eligibility at 12 tertiary neurology centres in Japan. Patients who satisfy the eligibility criteria are randomised (1:1) to receive thalidomide (100–300 mg daily) plus dexamethasone (12 mg/m^2 on days 1–4 of a 28-day cycle) or placebo plus dexamethasone. Both treatments were administered for 24 weeks (six cycles; randomised comparative study period). Patients who complete the randomised study period or show subacute deterioration during the randomised period participate in the subsequent 48-week open-label safety study (long-term safety period). The primary end point of the study is the reduction rate of serum VEGF levels at 24 weeks.

Ethics and dissemination: The protocol was approved by the Institutional Review Board of each hospital. The trial was notified and registered at the Pharmaceutical and Medical Devices Agency, Japan (No. 22-1716). The J-POST Trial is currently ongoing and is due to finish in August 2015. The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and will also be disseminated to participants.

Strengths and limitations of this study

- This study is the first randomised control trial for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome and provides a major turning point in its therapeutic approach, as there is no other randomised or non-randomised controlled trial because of the rarity and severity of the disease.
- This trial will include patients with POEMS syndrome who represent close to 10% of the entire Japanese patient population; thus, the results are generalisable.
- This placebo-controlled trial can evaluate the efficacy and safety of thalidomide without biases.
- The natural history of the disease remains partially unclear.
- This trial employs a surrogate instead of a hard end point, which is the reduction rate of serum vascular endothelial growth factor levels over 24 weeks, as the primary end point; the adequacy of the surrogate end point should be validated in this study and future trials.

Trial registration number: UMIN000004179 and JMA-IIA00046.

INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS) syndrome is a rare paraneoplastic disorder characterised by POEMS.[1] A Japanese national survey conducted in 2003 showed that its prevalence is 0.3/100 000 population.[2] Although the pathophysiology of POEMS

remains unclear, plasma cell dyscrasia and the related overproduction of the vascular endothelial growth factor (VEGF) are assumed to play a central role in the disorder.[3 4] Moreover, VEGF levels are characteristically elevated in POEMS.[3 5 6] VEGF levels were used recently as surrogate markers to evaluate disease activity,[7–10] because it sometimes takes several years to evaluate therapeutic effects in POEMS syndrome on the basis of hard end points, such as relapse-free survival or overall survival.[10 11]

The prognosis of POEMS syndrome was poor in the 1980s.[12 13] A large retrospective cohort study conducted in Japan reported that 38 of 58 patients who were treated mainly with corticosteroids died after a mean survival period of 33 months.[12] Since around 2000, the prognosis of POEMS has been considerably improved by the successful application of treatments for multiple myeloma, such as high-dose chemotherapy with autologous stem cell transplantation (HDCT with ASCT) or immunomodulatory drugs.[7–9 11 14] Currently, the therapeutic algorithm is the use of HDCT with ASCT as the first-line therapy, whereas patients who are not suitable for transplantation are treated with thalidomide or lenalidomide with dexamethasone. However, there is no established evidence of the efficacy of the new therapeutic interventions for POEMS, because the literature on these treatments includes only retrospective case reports or case series,[15] or open single-arm study,[16] because of the rarity and severity of the disease.

In addition, thalidomide, which is one of the standard treatment options for multiple myeloma, can suppress VEGF production and tumour proliferation.[17] Previous case reports or case series reported that thalidomide improved or stabilised the clinical symptoms in patients with POEMS syndrome and decreased serum VEGF levels,[8 18 19] and that it could be safely administered to patients who were not eligible for HDCT with ASCT because of older age or poor condition. However, randomised clinical trials are essential to investigate the efficacy and safety of new therapeutic interventions and to establish evidence and logical therapeutic strategies. Therefore, we designed the Japanese POEMS Syndrome with Thalidomide (J-POST) Trial, which is a phase II/III multicentre, double-blinded, randomised, controlled trial that aims to compare the efficacy and safety of a 24-week treatment with thalidomide with that of a placebo in POEMS syndrome, followed by a 48-week open-label safety study.

Objectives

We examined the hypothesis that POEMS syndrome is a paraneoplastic disorder associated with plasma cell dyscrasia, and that a therapeutic approach for multiple myeloma using thalidomide and dexamethasone can also be effective for treating POEMS. In addition, we investigated the feasibility of a randomised control study of POEMS syndrome and validated the assessments of the therapeutic effects.

METHODS

Trial design

The J-POST Trial is a 24-week multicentre, double-blinded, placebo-controlled randomised clinical trial of treatment of POEMS syndrome using thalidomide and dexamethasone (randomised comparative study period), followed by a 48-week open-label safety study (long-term safety period). Screening is undertaken within 28 days of randomisation to assess eligibility and collect baseline data. Patients who satisfy the eligibility criteria are randomly assigned (1:1) to receive thalidomide (100–300 mg daily) and dexamethasone (12 mg/m^2 on days 1–4 of a 28-day cycle) or placebo and dexamethasone. Patients who complete the randomised comparative study period or show subacute deterioration within the first 24 weeks participate in the subsequent 48-week open-label safety study. After this, a 4-week post-treatment observation period is scheduled. The primary end point of the randomised comparative study period is centrally assessed in the full analysis set of the reduction rate in VEGF levels at 24 weeks, and that of the long-term safety period is adverse events (AEs) associated with thalidomide. A schematic depiction of the trial design is summarised in figure 1.

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

Inclusion criteria

1. POEMS syndrome diagnosed according to published diagnostic criteria as 'Probable' or 'Definite' (box 1[20]).
2. Age ≥20 years.
3. Eastern Cooperative Oncology Group Performance Status of 0–3.
4. Overall score on the neuropathy limitation scale of 0–9.
5. Any of the following laboratory abnormalities: serum alanine aminotransferase or aspartate aminotransferase levels >4 times the normal upper limit; creatinine levels >1.5 times the normal upper limit.
6. Hospitalisation at the initiation of the randomised comparative study period and of the long-term safety period.
7. Regular clinic visits every 4 weeks.
8. No clinically significant ECG abnormality.
9. Signed written informed consent form.
10. Ineligibility for HDCT with ASCT during the study period.
11. Informed consent to thalidomide education and risk management system.

Exclusion criteria

1. Use of thalidomide, melphalan or bortezomib within 24 weeks of providing informed consent.
2. Unstable patients.

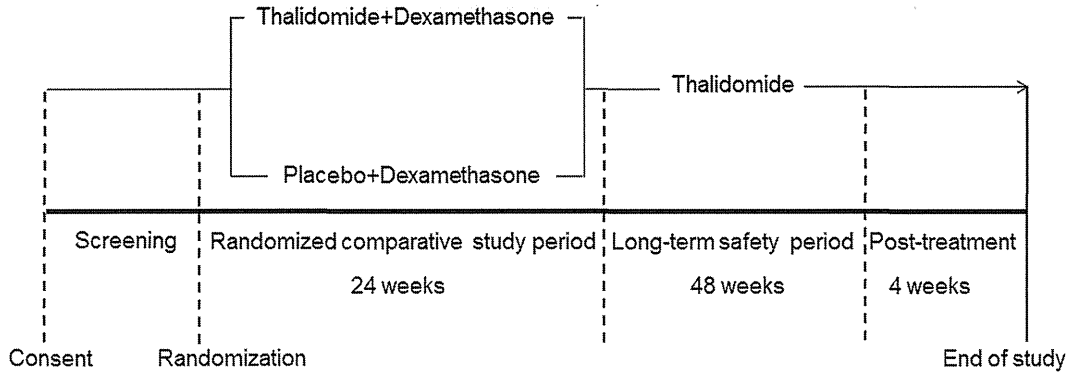

Figure 1 Schematic depiction of the trial design. Eligible participants are randomly assigned to a 24-week treatment of thalidomide (100–300 mg daily) plus dexamethasone (12 mg/m^2 on days 1–4 of a 28-day cycle) or placebo plus dexamethasone (randomised comparative study period). Patients who complete the randomised comparative study period or show subacute deterioration within the first 24 weeks participate in the subsequent 48-week open-label safety study (long-term safety period).

3. Oral or intravenous use of steroids within 4 weeks of providing informed consent.
4. Females who are pregnant or desire childbearing. Males who desire fertility.
5. Other serious and unstable medical conditions, such as cardiac failure, renal failure, liver failure, bleeding ulcers, ileus and uncontrolled diabetes.
6. Malignancy other than POEMS syndrome.
7. Known allergy to thalidomide or dexamethasone.
8. Serious mental disorder.
9. Use of any other experimental drug or therapy within 12 weeks of providing informed consent.
10. Use of prohibited drugs (other than β-blockers) or therapy within 4 weeks of the baseline.
11. Receiving a judgement of inappropriateness for the study.

Box 1 Diagnostic criteria of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome (modified from Misawa and Kuwabara[20])

Major criteria
- (a) Polyneuropathy
- (b) Monoclonal plasma cell proliferative disorder
- (c) Elevation of serum vascular endothelial growth factor levels

Minor criteria
- (d) Sclerotic bone lesions
- (e) Castleman disease
- (f) Organomegaly (hepatosplenomegaly or lymphadenopathy)
- (g) Oedema (oedema, pleural effusion or ascites)
- (h) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid or pancreatic)*
- (i) Skin changes (hyperpigmentation, hypertrichosis, plethora, cyanosis, haemangiomata or white nails)
- (j) Papilloedema
- (k) Thrombocytosis and/or polycythaemia

Definite POEMS syndrome: three major criteria and at least one minor criterion.
Probable POEMS syndrome: two major criteria, with at least one minor criterion.
*Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

Recruitment

This trial was declared and registered at the Pharmaceuticals and Medical Devices Agency in September 2010. Recruitment into the trial started in November 2010 and ended in February 2014, or until a total of 24 participants had been recruited. The treatment follow-up of the participants is currently ongoing and the last visit of the last patient is due to take place in August 2015. This study is being conducted at 12 tertiary neurology centres in Japan.

Sample size calculation

Twenty-four patients will be randomised and included in the study. This sample size was based on results from our previous studies[8 13] and the database of patients with POEMS syndrome; therefore, the estimated values of the reduction rate of serum VEGF level over 24 weeks were 0.55 (SD=0.21) after thalidomide–dexamethasone treatment and 0.35 (SD=0.20) after melphalan–prednisone treatment. Assuming a group difference of 0.35 (SD=0.25), 10 patients per arm will provide >80% power to detect a difference in the reduction rate of serum VEGF levels between thalidomide and placebo treatment for at least 24 weeks using a two-sided, two-sample t test at a 5% level of significance. Thus, to allow for a 20% dropout rate, 12 participants are required per group, for a total of 24 participants in the study.

Allocation

A registration form for an eligible patient will be sent by the investigators to the registration centre at EPS Associates Co, Ltd (by Fax). Registration and allocation will be implemented at the registration centre. Eligible patients who provide written informed consent will be

randomised to either thalidomide or placebo at a ratio of 1:1 by a computer program located at the registration centre, using a minimisation method[21 22] with biased coin assignment balancing on serum VEGF levels (≤3000 or >3000 pg/mL) and the evidence of pleural effusion (yes or no) at the screening test. The trial medication (with a unique number) will be distributed by the coordinating investigator to each hospital at the start of the trial. Investigators will prescribe the trial medication according to the number allocated at the registration centre.

Blinding

Participants and study personnel will be blinded to thalidomide or placebo treatment until the code is opened. Placebo capsules are indistinguishable in appearance from the thalidomide capsules. Serum VEGF levels will be measured at the central laboratory (SRL Medisearch Inc, Tokyo, Japan) and will also be masked to participants and study personnel from the baseline measurement to the opening of the code.

In case of emergencies for which it becomes necessary to unmask the blinding to make an adequate treatment decision, the blinding can be lifted by the investigator if deemed necessary. Patients in whom the blinding has been lifted will be removed from the trial immediately.

Interventions

Randomised comparative study period

Each treatment cycle will consist of 4 weeks (days 1–28), and thalidomide, or placebo, and dexamethasone will be administered for 24 weeks (six cycles). Thalidomide or placebo will be given on days 1–28, and dexamethasone will be administered at a dose of 12 mg/m^2 on days 1–4. The trial medication will be initiated on the randomisation day at a dosage of one capsule containing 100 mg of thalidomide or placebo, to be administered at bedtime every 2 days. The dose will increase to one capsule daily on day 8 and two capsules daily on day 15, and participants will continue to take two capsules daily after the titration period, if there is no haematological or skin toxicity that exceeds the Common Terminology Criteria for Adverse Events (CTCAE) of grade 3. The administration of thalidomide or placebo can be decreased and then discontinued as required during the study period, in cases that exhibit development of haematological or skin toxicity that exceeds the CTCAE of grade 3, or other AEs, for which investigators assume that dose reduction is appropriate.

Patients who experience subacute worsening of POEMS syndrome with subacute capillary leak-like symptoms (ie, 5 kg/month of weight gain or pleural effusion increase) or evident deterioration of neuropathy (ie, increase in the total score on the overall neuropathy limitation scale of >2) will promptly be shifted from the randomised comparative period to the long-term safety period.

Long-term safety period

Each treatment cycle will consist of 4 weeks (days 1–28) and only thalidomide will be administered for 48 weeks (12 cycles). The trial medication will be initiated on the first day of the long-term safety period at a dosage of one capsule (100 mg) of thalidomide, to be administered at bedtime every 2 days. The dose will increase to one capsule daily on day 8 and two capsules daily on day 15, and participants will continue to take two capsules daily after the titration period if there is no haematological or skin toxicity that exceeds the CTCAE of grade 3. The administration of thalidomide or placebo can be decreased and then discontinued as required during the study period, if there is haematological or skin toxicity that exceeds grade 3 in the CTCAE, or other AEs, for which investigators assume that dose reduction is appropriate.

Patients who experience subacute worsening of POEMS syndrome with subacute capillary leak-like symptoms (ie, 5 kg/month of weight gain or pleural effusion increase) or evident deterioration of neuropathy (ie, increase in the total score on the overall neuropathy limitation scale >2) will be treated with three capsules of thalidomide. If patients show further deterioration, 12 mg/m^2 of dexamethasone will be given to patients on days 1–4 of each cycle, in combination with thalidomide.

Treatment compliance

To evaluate treatment compliance, the number of capsules (thalidomide or placebo) remaining in each supply prescribed for patients will be counted.

Concomitant medication

The drugs or therapies, that is, anticancer agents other than thalidomide, radiotherapy or oral or intravenous steroids, are not permitted throughout the study.

Outcomes

Randomised comparative study period

The primary outcome measure is the reduction rate of serum VEGF level over 24 weeks after treatment by mutual agreement between the Pharmaceutical and Medical Devices Agency (PMDA) and the J-POST Trial, because VEGF levels are considered as a surrogate marker used to evaluate disease activity in POEMS syndrome.[7–10] The definition of the reduction rate is as follows: serum VEGF level reduction rate=(VEGF level at the baseline–VEGF level at 24 weeks)/VEGF level at the baseline. The secondary end points include changes in serum VEGF levels, the achievement of a normal range of serum VEGF level (<1000 pg/mL), motor functions (sum scores of manual muscle testing (MMT), grip and overall neuropathy limitation scale), parameters of nerve conduction studies (motor conduction velocity (MCV), compound muscle action potential (CMAP) amplitude and F-wave latency), M-protein levels (serum and urine), pleural effusion, vital capacity, body weight and quality of life (QOL, SF-36)[23 24] as well as AEs.

Long-term safety period

The primary outcome measure will be AEs, because the major aim of the long-term safety period is to investigate the safety of thalidomide administration for 12–18 months. The secondary end points include changes in serum VEGF levels, the achievement of a normal range of serum VEGF levels (1000 pg/mL), motor functions (MMT sum score, grip and overall neuropathy limitation scale), parameters of nerve conduction studies (MCV, CMAP amplitude and F-wave latency), M-protein levels (serum and urine), pleural effusion, vital capacity, body weight and QOL (SF-36).

Data collection

Trial visits and examinations

The trial is divided into four periods: (1) screening; (2) randomised comparative study period (24 weeks, six cycles); (3) long-term safety study period (48 weeks, 12 cycles); and (4) post-treatment observation period. Each treatment cycle consists of 4 weeks (days 1–28), and patients will make visits on day 1 of each cycle during the study period. For all female participants of reproductive age, pregnancy tests will be conducted every 28 days. The schedule for the study visits and data collection is summarised in table 1.

Data management, monitoring and auditing

The investigators (or their delegates) will maintain individual records for each patient as source data, which include a log of informed consent, medical records, laboratory data and other records or notes, as appropriate. All entries in the case report form (CRF) must be backed up by the relevant source data. All source data will be kept according to good clinical practice (GCP). CRFs must be completed in a timely manner.

All data are collected by the independent data management centre that was established for the present study. There will be no direct communication between POEMS investigators and the Coordinating Data Centre. The clinical data entry (double data entry), coding, data management and reporting will be performed using the data management system CLiSSS (Medical Edge Inc, Tokyo, Japan). Data management will be carried out according to the standards of procedure of the trial.

A monitor will confirm that the investigational team is adhering to the protocol and GCP, that data are being accurately recorded in CRFs, that AEs have been properly documented on CRFs, that severe AEs (SAEs) have been forwarded to the coordinating investigator and the provider of the investigational product, and that the SAEs that met criteria for reporting have been forwarded to the Institutional Review Board (IRB). An interim analysis will not be performed.

The study may be audited or inspected by the provider of the investigational product or PMDA. In case of an audit, the investigators must make all study documentation available to the auditor. If an audit or inspection occurs, the investigators at the study site must discuss the findings and any relevant issues.

Harms

Investigators must record all AEs in the patients' CRFs. The National Cancer Institute's CTCAE (V.4.0) will be used to grade each AE. All AEs are to be followed up

Table 1 Schedule of data collection

		Randomised comparative study period					Long-term safety period					
	Screening	C1 D1	D8	C2 D1	C3–6 D1	EOT	C1 D1	D8	C2 D1	C3–6 D1	EOT	Follow-up 4 weeks after EOT
Informed consent	X											
Clinical assessment*	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs†	X	X	X	X	X	X	X	X	X	X	X	X
Blood/urine tests‡	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine tests (fasting)		X					X					
VEGF measurements	X	X		X	X	X	X		X	X	X	X
Chest X-ray	X	X		X	X	X	X		X	X	X	
ECG	X	X	X		X	X	X	X		X	X	
CT	X	X			X	X	X			X	X	
Nerve conduction studies		X			X	X	X			X	X	
Respiratory function tests		X				X	X				X	
SF-36		X				X	X				X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Pregnancy tests§	X	X	X	X	X	X	X	X	X	X	X	X

*Clinical assessment: complete history/examination (screening), focused history/examination (during study period).
†Vital signs: heart rate, blood pressure, weight.
‡Blood/urine tests include free-light chain and immunofixation of M-protein on D1 of C1 and 3 of randomised, comparative study period and on D1 of C1 and 3 of long-term safety period.
§Pregnancy tests will be examined in all female participants of reproductive age every 28 days.
C, cycle; D, day; EOT, end of treatment; SF-36, MOS Short-Form 36-Item Health Survey; VEGF, vascular endothelial growth factor.

continually during their course until resolution, or for 4 weeks after the end of the trial. All SAEs must be reported to all investigators and discussed through a web-based AE reporting system; SAEs that were not reported previously will be reported to PMDA.

Statistical methods

The analyses of the primary and secondary outcomes will be performed in the full analysis set. For the baseline variables, summary statistics will be constructed using frequencies and proportions for categorical data, and means and SDs for continuous variables. Patient characteristics will be compared using Fisher's exact test for categorical outcomes, and t tests or the Wilcoxon rank sum test for continuous variables, as appropriate.

For the primary analysis, which will be aimed at comparing treatment effects, the least squares means (LSMeans) and their 95% CI, which are estimated using analysis of covariance (ANCOVA) of the reduction rate of serum VEGF levels (untransformed) on week 24, will be compared between the thalidomide and placebo groups using an ANCOVA model, taking into account the variation caused by treatment effects and using the baseline serum VEGF levels (≤3000 or >3000 pg/mL) and evidence of pleural effusion as covariates. To compare the treatment groups, the difference in LSMeans and the 95% CIs will be expressed as a proportion of the reference treatment LSMean. The primary analyses will be performed in the full analysis set without imputing missing observations. As a sensitivity analysis, a mixed-effect model for repeated measures (MMRM) and the last observational carried forward (LOCF), and the multiple imputation methods will be applied to examine the effect of missing data. The secondary analysis will be performed in the same manner as the primary analysis.

All comparisons are planned and all p values will be two sided. p Values of <0.05 will be considered statistically significant. All statistical analyses will be performed using the SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA). This statistical analysis plan was developed by the chief investigator and the statistician at Chiba University before completion of the patient recruitment and data collection.

Ethics and dissemination

Research ethics approval and protocol amendments

Substantial amendments of the study protocol must be approved by IRB. The trial was notified and registered at PMDA (No. 22-1716), and at the UMIN Clinical Trials Registry (UMIN000004179) and JMACCT Clinical Trials Registry (JMA-IIA00046).

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and on alternative therapeutic choices using an informed consent approved by IRB. A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrolment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form.

Confidentiality

To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

Dissemination

The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and will also be disseminated to participants.

DISCUSSION

The J-POST Trial is the first randomised control trial (RCT) to investigate the efficacy and safety of a therapeutic agent for POEMS syndrome. RCTs are essential to establish quality evidence, although it is generally difficult to conduct RCTs for rare and severe diseases, such as POEMS syndrome, from the viewpoints of designing appropriate study schema and recruiting patients. This trial can be a prototype RCT for POEMS syndrome and contribute considerably to the future evolution of treatment for this syndrome.

The application of therapeutic interventions for multiple myeloma to POEMS syndrome has quite improved its prognosis.[15 20] In the near future, the number of new therapeutic choices for multiple myeloma, such as next-generation immunomodulatory drugs, proteasome inhibitors, signal transduction inhibitors and molecular targeted drugs, will be available and may be effective for POEMS syndrome.[20] Prospective clinical trials are vital to establish evidence-based treatment strategies for the management of the increasing therapeutic choices. Moreover, RCTs are optimal to prove the efficacy and safety of each agent, if possible.

There were some limitations to this study. First, the natural history of POEMS syndrome remains to be elucidated. Patients with POEMS syndrome generally show subacute deterioration and cannot walk independently within 1 year of the onset of the disease.[25] Conversely, in some patients, the disease progresses very slowly. At present, we cannot foresee disease courses exactly at the initial diagnosis of a patient. Recruiting patients with various disease courses into the trial can affect the results substantially. To avoid the recruitment of patients with specific disease course into either the thalidomide or placebo group, randomisation will be stratified according to VEGF levels, which can reflect disease activity, and pleural effusion, which can sometimes be life-threatening in POEMS syndrome.

The second limitation was that this trial employed a surrogate marker, instead of a hard end point, that is, the reduction rate of serum VEGF level over 24 weeks

after treatment, as the primary outcome. Markedly elevated serum VEGF levels are specifically found in patients with POEMS syndrome,[3 5 6] and the characteristic features of this syndrome (eg, pleural effusion, oedema or angiomata) are consistent with the physiological effects of VEGF, such as increased vascular permeability and angiogenesis.[26] VEGF levels generally decrease in response to treatment and are considered to reflect disease activity.[7–10] In this study, we will also prospectively investigate changes in clinical observations and laboratory parameters over 18 months, to test the adequacy of serum VEGF levels as a surrogate end point.

Close observational studies and an appropriate rationale are essential for good-quality prospective clinical trials, and enable the conduct of RCTs even in rare and fatal diseases. This study may be a major turning point in the therapeutic approach for POEMS syndrome, as well as a model to establish evidence in rare diseases.

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Contributors All authors made a significant contribution to the conception and design of the study protocol. SK designed the original concept. The protocol was written by KK, SM, YS and HH, and it was critically reviewed by SK, IY, IN, MN, S-il, GS, SK, NK, TK, JK and OW. All authors gave approval for the publication.

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Competing interests The investigational products are provided by the Fujimoto Pharmaceutical Corporation.

Ethics approval The protocol was approved by the Institutional Review Board of each participating hospital.

Provenance and peer review Not commissioned; internally peer reviewed.

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Vascular endothelial growth factor as a predictive marker for POEMS syndrome treatment response: retrospective cohort study.

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Vascular endothelial growth factor as a predictive marker for POEMS syndrome treatment response: retrospective cohort study

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ABSTRACT

Objective: POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome is a rare multisystem disease characterised by plasma cell dyscrasia and overproduction of vascular endothelial growth factor (VEGF). VEGF is assumed to be useful in monitoring disease activity, because VEGF levels usually decrease after treatment. However, there is no study to investigate whether the extent of decrease in VEGF correlates with clinical outcome. We tested the predictive efficacy of serum VEGF levels in POEMS syndrome.

Method: This was an institutional review board approved retrospective observational cohort study of 20 patients with POEMS monitored regularly for more than 12 months (median follow-up, 87 months) after treatment onset using our prospectively accumulated database of POEMS from 1999 to 2015. Patients were treated by autologous peripheral blood stem cell transplantation or thalidomide administration. Serum VEGF was measured by ELISA. Outcome measures included clinical and laboratory findings and relapse-free survival.

Results: Serum VEGF levels decreased rapidly after treatment, and stabilised by 6 months post treatment. Patients with normalised serum VEGF levels (<1040 pg/mL) at 6 months showed prolonged relapse-free survival (HR=12.81, 95% CI 2.691 to 90.96; p=0.0001) and greater later clinical improvement. The rate of serum VEGF reduction over the first 6 months post treatment correlated with increased grip strength, serum albumin levels, and compound muscle action potential amplitudes at 12 months.

Conclusions: Serum VEGF level at 6 months post treatment is a predicative biomarker for disease activity and prognosis in POEMS syndrome. Serum VEGF could be used as a surrogate endpoint for relapse-free survival or clinical or laboratory improvement of POEMS syndrome for clinical trials.

Strengths and limitations of this study

- This study showed the extent of serum vascular endothelial growth factor (VEGF) reduction after treatment significantly correlates with the prognosis in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome.
- VEGF can be used as a surrogate marker in prospective clinical trials for POEMS syndrome.
- This is a retrospective study, including a small number of patients of different background and age.

INTRODUCTION

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome is a rare (prevalence 0.3 per 100 000) multisystemic disorder associated with plasma cell dyscrasia.[1 2] Potentially fatal clinical manifestations include progressive demyelinating polyneuropathy leading to tetraplegia.[3–5] Overproduction of vascular endothelial growth factor (VEGF), a multifunctional cytokine that induces angiogenesis and microvascular hyperpermeability,[6] may be involved in the pathogenesis of many POEMS symptoms. Serum VEGF is markedly and specifically elevated in this syndrome,[7–10] and major diagnostic criteria include increased VEGF.[11–13] Moreover, serum VEGF concentration usually decreases following successful therapeutic intervention.[14–17] However, no study has investigated whether changes in VEGF levels after treatment are predictive of clinical improvement or outcome.

New therapeutic interventions, such as autologous peripheral blood stem cell transplantation and immunomodulatory drug regimens, have improved POEMS prognosis,[14 15 18 19] but comparative evaluations of treatment efficacy are lacking. Most POEMS studies are retrospective case series or case reports rather than prospective randomised controlled clinical trials due to the rarity of

this disease.[12] A reliable early biomarker of long-term outcome could facilitate clinical trials even with a limited patient sample. Therefore, we examined whether VEGF levels are predictive of longer-term clinical improvement.

METHODS

Subjects

This observational study was approved by the institutional review board of Chiba University Graduate School of Medicine. The diagnosis of POEMS was established using the published criteria.[12] Study subjects for this retrospective cohort study were drawn from our database of 85 consecutive patients with POEMS (57 men) treated from 1999 to 2015. From this database, we identified 21 consecutive patients who started primary POEMS syndrome treatment, peripheral blood stem cell transplantation or thalidomide, during the 10-year period 1999–2009 because in 2010 we began an ongoing clinical trial of POEMS syndrome in which serum VEGF levels are blinded.

From the 21 patients, we excluded one patient treated with bevacizumab (anti-VEGF monoclonal antibody) because bevacizumab strongly suppresses VEGF levels for several months. In the 20 patients, VEGF levels were measured regularly (at least once every 3–6 months) for more than 1 year after transplantation or thalidomide treatment and the median follow-up period is 87 months (range 24–133 months). Clinical signs (performance status, overall neuropathy limitation scale and grip strength (sum of both hands)) and blood tests were checked at each visit and nerve conduction studies were performed every 3–6 months. Eight patients were pretreated with low to moderate dose steroids (n=7) or immunoglobulin (n=1) prior to transplantation or thalidomide. Clinical and laboratory profiles of the 20 patients are shown in table 1. Changes in serum VEGF levels after treatment were measured and correlations with clinical/laboratory findings, relapse-free survival and complete remission were calculated. We defined relapse as clinical deterioration attributable to POEMS syndrome, such as extravascular overload (oedema/effusions/ascites) or neuropathy, and censoring was defined as the last visit during the observation period. Complete remission was defined according to the International Myeloma Working Group criteria: negative immunofixation with disappearance of any plasma cytomas and >5% plasma cells in the bone marrow.[17 20] One author (SM) selected the patients from the database and reviewed medical records. YS, who was blinded to the clinical information, mainly performed statistical analysis.

Treatments for POEMS syndrome

Patients were treated with transplantation (n=12) or thalidomide and dexamethasone (n=8). Autologous peripheral blood stem cell collection was performed after mobilisation by subcutaneous granulocyte colony-stimulating factor with or without high-dose cyclophosphamide (2 g/m^2/day for 2 consecutive days). High-dose melphalan chemotherapy (140–200 mg/m^2) and stem-cell transplantation were performed approximately 1 month after blood cell collection according to the standard treatment regimen for multiple myeloma. Melphalan dose was reduced in patients with performance status 4 (completely disabled). The median follow-up period after transplantation was 90 months (range 35–133 months). Combination thalidomide (100–300 mg/day on days 1–28) and dexamethasone (12 mg/m^2 on days 1–4) was administered every 4 weeks for 19–42 cycles (median 32 cycles). The median follow-up period after thalidomide administration was 87 months (range 24–106 months).

VEGF measurements

Serum VEGF levels were measured by ELISA commercially (Special Reference Laboratory Co., Tokyo, Japan).

Table 1 Patient characteristics (n=20)

	Auto-PBSCT (n=12)	Thalidomide (n=8)
Clinical profiles		
Age (years)	48 (36–61)	69 (59–84)
Gender (male:female)	9:3	5:3
Time from symptoms to therapy (months)	17 (2–120)	25 (4–101)
Performance status	1 (1–4)	2 (1–3)
Overall Neuropathy Limitation Scale	5 (1–11)	6 (2–9)
Laboratory data		
Albumin (g/dL)	3.8 (2.7–4.5)	3.4 (2.7–3.9)
Creatinine (mg/dL)	0.7 (0.5–1.2)	0.9 (0.4–2.0)
Immunoglobulin (IgA:IgG)	4:6	2:5
Vascular endothelial growth factor	2950 (126–7870)	2520 (1430–7970)
Nerve conduction study (median nerve)		
CMAP amplitude (mV)	5.3 (0–12.8)	5.2 (0.1–9.4)
Motor conduction velocity (m/s)	33.0 (23–45)	26 (14–48)

Data are given as median (range).
CMAP, compound muscle action potential; PBSCT, peripheral blood stem cell transplantation.

The cut-off values for diagnosis of POEMS was established using data from 50 untreated patients with POEMS (33 men; age range 34–76 years) from our retrospective cohort and samples from 120 healthy subjects (61 men; age range 21–79 years). The cut-off value for diagnosis (1040 pg/mL) was defined as the point with 100% sensitivity and 99% specificity by plotting receiver operating characteristic curves.

Statistical analyses

For the baseline variables, summary statistics were constructed employing frequencies and proportions for categorical data, and means and SDs for continuous variables. Univariate analyses were carried out using the t test or Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. For time-to-event outcomes, the Kaplan–Meier method was used to estimate relapse-free survival for each group, and the difference in survival between groups was compared by the log-rank test. The HRs and 95% CIs were estimated by the Cox proportional hazards model.

All comparisons were planned and the tests were two sided. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using JMP, Japanese V.5.1.1 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

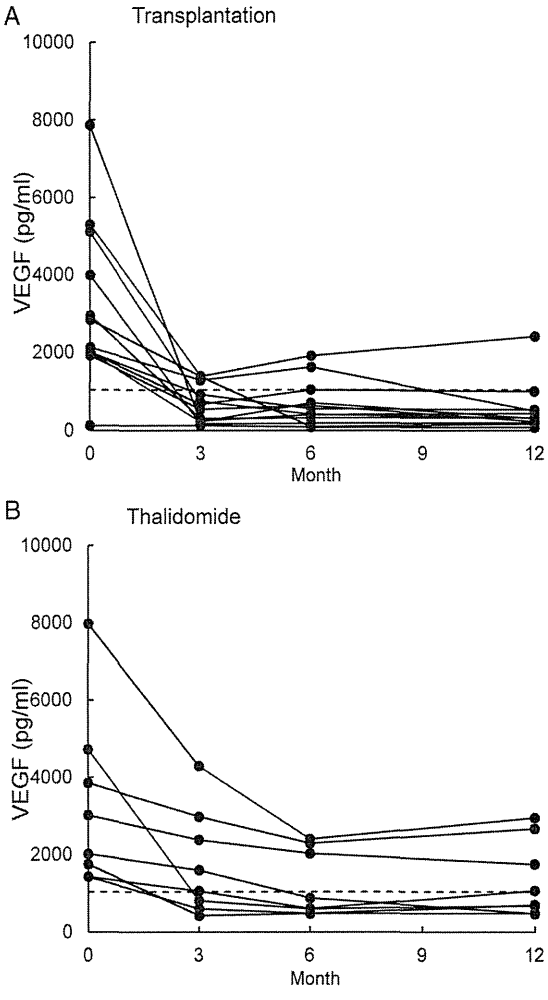

Figure 1 Changes in serum vascular endothelial growth factor (VEGF) after treatment. (A) Autologus peripheral blood stem cell transplantation with high-dose chemotherapy (n=12). (B) Thalidomide–dexamethasone therapy (n=8).

RESULTS

Changes in VEGF levels after treatment and relapse-free survival

Before the start of autologous peripheral blood stem cell transplantation or thalidomide treatment for POEMS syndrome, serum VEGF was elevated above the cut-off value (1040 pg/mL) in all but one patient. The one pretreated for 6 months with moderate-dose steroid (prednisone 20–30 mg daily) exhibited low VEGF levels throughout the study period following primary POEMS syndrome treatment (transplantation). Serum VEGF levels decreased steadily over 6 months after primary treatment and eventually stabilised in all patients (figure 1). Patients treated by transplantation (n=12) had a mean ±SD baseline VEGF of 3186±2072 pg/mL, decreasing to 668±481 pg/mL at 3 months, 664±584 pg/mL at 6 months, and 541±635 pg/mL at 12 months post treatment. The rate of decrease among patients treated with transplantation was steeper than those treated with thalidomide (3273±2244 pg/mL at baseline, 1770±1352 pg/mL at 3 months, 1223±857 pg/mL at 6 months, and 1350 ±993 pg/mL at 12 months). All patients with serum VEGF≥1040 pg/mL (cut-off value) at 6 months post treatment relapsed with a median time of 36 months. The Kaplan–Meier estimates of relapse-free survival at 3 years were 93% in patients with VEGF levels <1040 pg/mL and 40% in patients with VEGF levels ≥1040 pg/mL

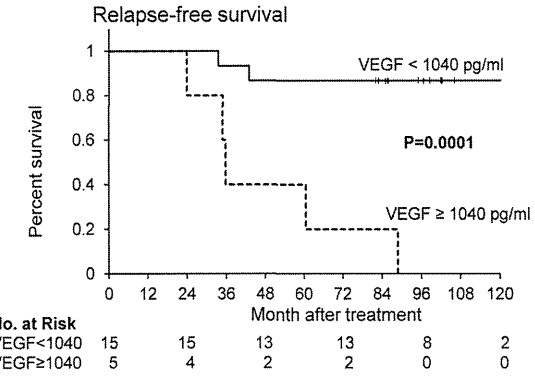

Figure 2 Kaplan–Meier plot for relapse-free survival. Patients with vascular endothelial growth factor (VEGF) <1040 pg/mL at 6 months after treatment showed significant longer relapse-free survival than patients with VEGF≥1040 pg/mL (HR=12.81, 95% CI 2.691 to 90.96; p=0.0001).

Table 2 Changes in clinical and laboratory parameters after treatment (n=20)

	A Baseline	B 6 months	C 12 months	p Value A vs B	p Value A vs C
Performance status	1.5 (1–4)	1 (1–4)	1 (1–4)	1.0	0.19
Overall Neuropathy Limitation Scale					
Arm scale	2 (0–4)	2 (0–4)	1 (0–4)	0.069	0.0016
Leg scale	3 (1–7)	3 (1–7)	2.5 (0–7)	0.15	0.025
Grip	28 (6–85)	32 (0–93)	40 (0–107)	0.052	0.014
Laboratory data					
Albumin (g/dL)	3.8 (2.7–4.5)	3.55 (2.7–4.8)	4.3 (2.7–5.1)	0.056	0.013
Creatinine (mg/dL)	0.77 (0.42–2.02)	0.77 (0.37–1.13)	0.84 (0.38–1.63)	0.13	0.44
Nerve conduction study (median nerve)					
CMAP amplitude (mV)	5.3 (0–12.8)	6.2 (0–14.1)	8.2 (0–4.6)	0.31	0.0005
Motor conduction velocity (m/s)	32 (17–48)	39 (20–50)	39 (20–50)	0.19	0.008

Data are given as median (range).
CMAP, compound muscle action potential.

at 6 months post treatment (HR=12.81; 95% CI 2.691 to 90.96; p=0.0001, figure 2). These findings suggest that suppression of serum VEGF levels to within the normal range at 6 months post treatment may prolong relapse-free survival. All of the seven patients with relapsed disease were treated with thalidomide. The complete remission rate did not differ significantly between the two groups.

VEGF reduction and clinical improvement

Significant clinical and laboratory improvement could not be detected at 6 months post treatment. However, at 12 months multiple clinical and laboratory parameters significantly improved (table 2). The extent of improvement in grip strength, serum albumin and compound muscle action potential amplitude of the median nerve were significantly greater in patients with VEGF levels <1040 pg/mL than in patients with serum VEGF ≥1040 pg/mL at 6 months post treatment (figure 3). In addition, rate of decrease over the first 6 months post treatment was correlated with the extent of clinical and laboratory improvements at 12 months (figure 4). These findings suggest that significant clinical and laboratory improvement can be obtained several months after VEGF levels decrease, and that the greater the decrease by 6 months post treatment, the greater the delayed improvement in laboratory findings and clinical outcome. No significant correlations between decreases in VEGF and improvement in performance status, overall neuropathy limitation scale, pleural effusion or creatinine could be detected.

DISCUSSION

We show that serum VEGF levels decreased and reached a plateau over the 6 months following treatment of peripheral blood stem cell transplantation or thalidomide. Patients with normal VEGF levels at 6 months post treatment showed significantly longer relapse-free survival and greater delayed clinical and laboratory improvements. The rate of reduction in serum VEGF over the first 6 months after treatment correlated with the extent of clinical and laboratory improvement at 12 months. These findings suggest that the extent of reduction in VEGF correlates with improvement of the disease and treatments for POEMS syndrome should aim to decrease serum VEGF within the normal range. In addition, the fact that decreased serum VEGF reached a plateau over 6 months after treatment indicates that at least 6 months are required to determine the effect of treatment, and a change in therapeutic strategy should be considered if VEGF levels do not decrease sufficiently at 6 months post treatment. This is the first study to demonstrate that serum VEGF level can be used as a surrogate biomarker to monitor disease activity and predict clinical outcome of POEMS syndrome. A reliable early predictive marker of long-term outcome will facilitate clinical trials for POEMS syndrome treatment given the inherent difficulty in larger scale prospective studies for such rare and severe diseases.

Since the first demonstration of elevated serum VEGF levels in POEMS syndrome patients,[7] numerous studies have confirmed that VEGF levels increase in untreated POEMS syndrome and decrease after treatment, implicating elevated VEGF in disease pathophysiology.[14–19] Indeed, the physiological effects of VEGF, such as vascular hyperpermeability and angiogenesis,[6] are consistent with the characteristic symptoms of POEMS syndrome (eg, pleural effusion, oedema or angiomata). However, whether lower VEGF levels after treatment represent suppression of the disease itself or a mere epiphenomenon had not been unequivocally demonstrated. The present study clearly shows that the extent of the decreases in VEGF reflects later clinical improvement; a greater reduction at 6 months post treatment predicts better prognosis at 1 year. Moreover, if VEGF levels are suppressed below the upper limit of the normal range, longer remission can be achieved. Therefore, treatment for POEMS should aim to control VEGF within the

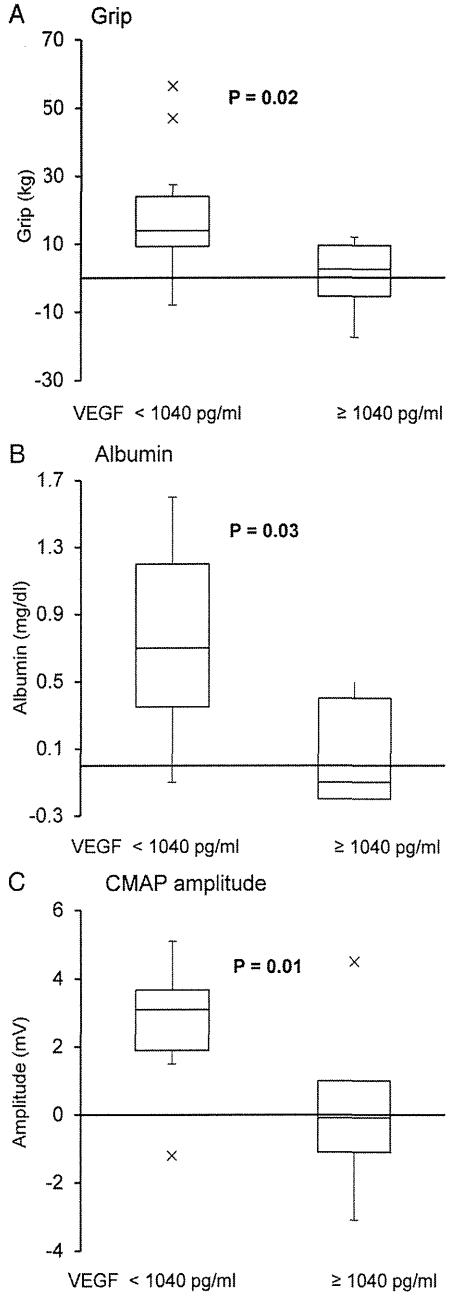

Figure 3 Changes in clinical or laboratory measures at 12 months post treatment. (A) Grip strength. (B) Serum albumin. (C) Compound muscle action potential (CMAP) amplitude of the median nerve. Patients with serum vascular endothelial growth factor (VEGF) <1040 pg/mL at 6 months after treatment showed significant improvements in all parameters compared with patients with VEGF ≥1040 pg/mL.

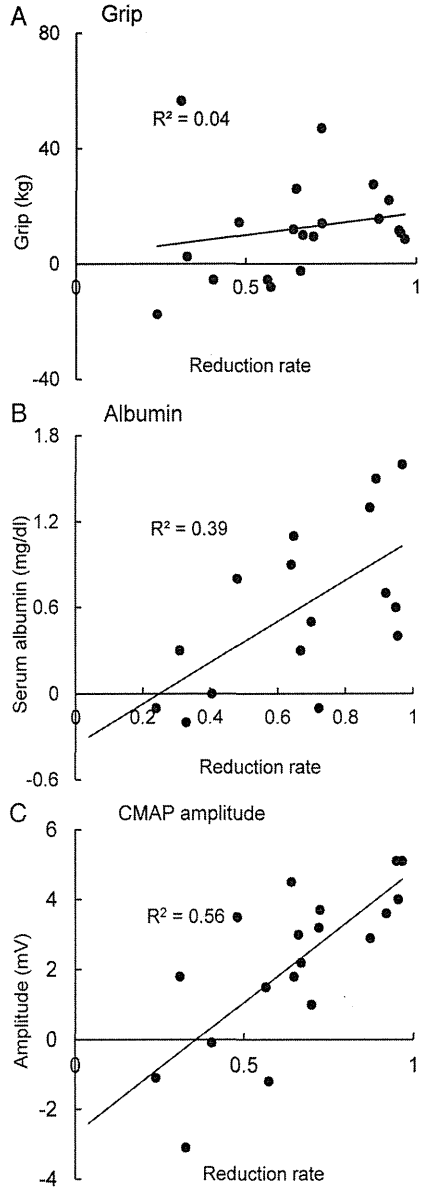

Figure 4 Correlation between reduction rate of vascular endothelial growth factor (VEGF) at 6 months after treatment and changes in grip strength (A), serum albumin (B), and CMAP amplitude of the median nerve (C) at 12 months after treatment. The grater the rate of VEGF decline at 6 months of treatment, the better the clinical and laboratory findings at 12 months.

normal range. These findings strongly suggest that overproduction of VEGF plays a central role in the pathophysiology of POEMS syndrome.

This retrospective study has several limitations. First, we retrospectively investigated a small number of patients with POEMS with different backgrounds. The difference in mean age of the two groups of studied patients (transplanted and thalidomide treated) may substantially influence treatment response and VEGF level. However, we aimed to study whether VEGF could be used as a predictive marker, irrespective of the patients' background and treatment modality. We believe that this was achieved by our data. Second, we investigated whether only serum VEGF levels reflect disease activity and prognosis of POEMS syndrome, or whether other proinflammatory cytokines, such as TNF-α, IL-6 and IL-12, are also upregulated during active disease and IL-12 levels decrease after treatment.[21]

Inhibition of VEGF alone by a monoclonal antibody (bevacizumab) does not appear to be effective, particularly in advanced cases,[22–24] further implicating other proinflammatory factors in disease progression. Future prospective studies are necessary to investigate which cytokines are most appropriate for monitoring disease activity. Third, the present study evaluated serum levels of VEGF, and it is controversial whether serum or plasma VEGF is a better indicator of disease activity.[11 17 25] While plasma level of VEGF is less affected by platelets, serum VEGF levels can be reflected from the serous and platelet compartments. Since the origin of VEGF in POEMS syndrome has not yet been clarified, VEGF stored in platelets may play an important role in the pathophysiology of POEMS syndrome. Therefore, we consider that monitoring serum VEGF may better indicate the total amount of VEGF in the patient.[26] However, further investigations may be required to evaluate the relationship between serum and plasma VEGF levels in the treatment course of POEMS syndrome.

The prognosis for patients with POEMS syndrome was very poor when only corticosteroids were available as treatments.[3 4] However, a number of case series and reports have demonstrated improved prognosis using treatments originally developed for multiple myeloma.[12 14 15 18 19] The next step is to perform well designed prospective clinical trials and establish evidence-based therapeutic guidelines.[12 13] To confirm the efficacy of a therapeutic intervention, so-called hard endpoints are expected, such as overall survival or progression-free survival. However, such studies take several years and require large sample sizes,[11 27] and are generally not feasible for rare diseases. Surrogate endpoints to assess therapeutic efficacy in a brief period could allow short-term clinical trials involving smaller patient groups. This study demonstrates that serum VEGF at 6 months post treatment can be used as a primary endpoint for POEMS syndrome treatment outcome. In addition, VEGF is suitable for an endpoint of clinical trials from the view point that VEGF measurement is quantitative and objective and can be blinded by measurement at a central laboratory.

Additional agents for multiple myeloma, such as proteasome inhibitors, monoclonal antibodies, cell cycle specific drugs, deacetylase inhibitors and signalling transduction pathway inhibitors will be available in the near future[28] and could be applied to POEMS syndrome.[13] While the adequacy of serum VEGF as a surrogate endpoint needs further confirmation, this marker may facilitate prospective clinical trials on the safety and efficacy of these newer drugs despite the rarity of this syndrome. In fact, we are now conducting a multicentre, double-blind and randomised controlled clinical trial[29] to evaluate the efficacy and safety of thalidomide for POEMS syndrome using the rate of VEGF decrease over 6 months post treatment as the primary endpoint (declared and registered to the Japan Pharmaceuticals and Medical Devices Agency).

Contributors SM and YS analysed the data. SM, YS, KK, HH and SK designed the research, collected and wrote the manuscript. SS, MB, FN, KS, YS, YI, KW, HA, CO, MT, ES and CN assisted in data collection and manuscript preparation. All authors approved the final draft of the paper.

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Ethics approval The protocol was approved by the institutional review board of Chiba University Graduate School of Medicine.

Provenance and peer review Not commissioned; internally peer reviewed

Data sharing statement No additional data are available.

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Acutely deteriorated extravascular volume overload during peripheral blood stem cell mobilization in POEMS syndrome: A case series with cytokine analysis

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Case Report

Acutely deteriorated extravascular volume overload during peripheral blood stem cell mobilization in POEMS syndrome: A case series with cytokine analysis

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ABSTRACT

We describe two cases of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome patients with deteriorated extravascular volume overload without increased levels of vascular endothelial growth factor after the administration of cyclophosphamide + granulocyte colony-stimulating factor for stem cell mobilization. We then measured the serum levels of 27 cytokines from these cases using a multiplex suspension array system. The analysis revealed the changes of cytokine profiles before cyclophosphamide + granulocyte colony-stimulating factor and after the development of capillary leak symptoms in both cases. This may improve our current level of understanding of the pathogenesis of POEMS syndrome not driven by vascular endothelial growth factor.

1. Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome is a rare plasma cell disorder characterized by the constituent ailments that comprise its name. Signs of extravascular volume overload, which are frequently observed in POEMS syndrome, are among the most common preterminal events in POEMS syndrome [1]. It has been speculated that elevated levels of vascular endothelial growth factor (VEGF) play a crucial role in inducing extravascular volume overload via angiogenesis and microvascular hyperpermeability [1,2]. However, discrepancies between disease activity and VEGF levels in POEMS syndrome patients have been reported [3]. Additionally, the efficacy of the anti-VEGF monoclonal antibody bevacizumab for POEMS syndrome patients has been a matter of controversy due to mixed study results [4–6]. Furthermore, several other cytokines, such as interleukin (IL)-6, IL-12, tumor necrosis factor-α, and hepatocyte growth factor, have been reported to be elevated in POEMS syndrome [7–9]. Therefore, VEGF may not be the driving force behind this disorder. Here we report two cases of patients with POEMS syndrome with acutely deteriorated extravascular volume overload without increased levels of VEGF after

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the administration of high dose cyclophosphamide (HD-CY) + granulocyte colony-stimulating factor (G-CSF) (CG) for peripheral blood stem cell (PBSC) mobilization. We then measured serum levels of 27 cytokines from these cases before and after CG using a multiplex suspension array system, and analyzed the changes in their cytokine profiles during their clinical courses.

2. Case 1

The first case (case 1) is a 61-year-old man who was diagnosed with POEMS syndrome and was referred to our institution in July 2008. His clinical course is shown in Fig. 1. The day of administration of G-CSF for PBSC collection is defined as day 0. The patient presented with monoclonal gammopathy (IgG-λ), a slight left pleural effusion, hepatosplenomegaly, and polyneuropathy with a performance status of 2. The level of serum VEGF was 8160 pg/mL on day minus 29. He was treated with high-dose dexamethasone (DEX: 40 mg/body; days minus 21 to minus 18), leading to an improvement in his systemic edema. He received HD-CY (2 g/m^2; days minus 13 to minus 12), followed by G-CSF (10 μg/kg; days 0–4) for PBSC collection. PBSC collection was performed on day 4. The required number of CD34$^+$ cells (5.12×10^6/kg) for autologous stem cell transplantation were harvested using the COBE Spectra cell separator (COBE Spectra, CaridianBCT, USA), although respiratory failure occurred 3 days after PBSC collection, and a computed

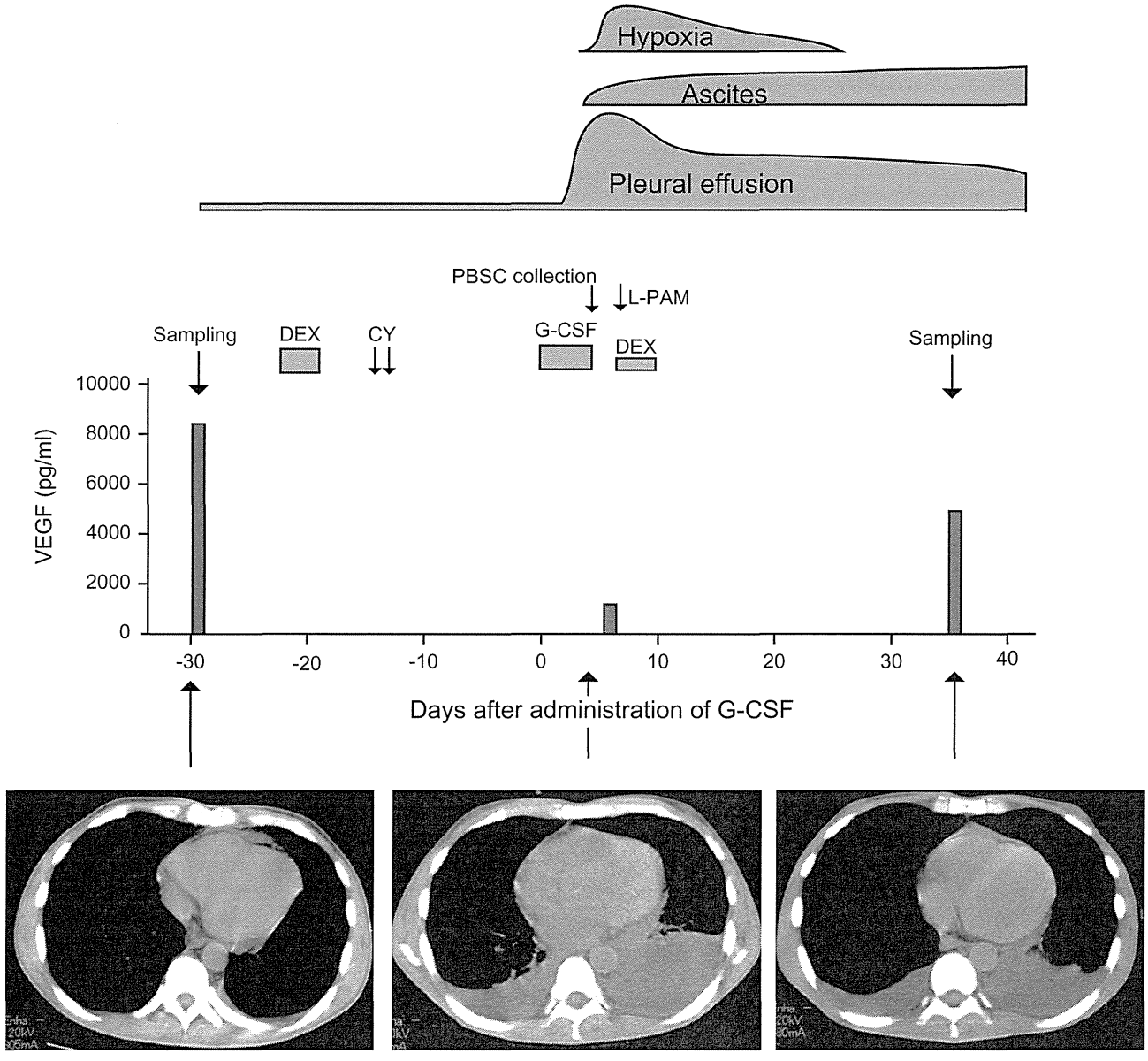

Fig. 1. Serial changes in computed tomography (CT) scan images and vascular endothelial growth factor (VEGF) level, and the therapeutic course of case 1. The sera sampling time points for the multiplex suspension array system are indicated by arrows. DEX, dexamethasone; CY, cyclosphosphamide; PBSC, peripheral blood stem cell; L-PAM, melphalan.

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