Safety and efficacy of thalidomide in patients with POEMS syndrome: a multicentre, randomised, double-blind, placebo-controlled trial

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Summary

Background **Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare cause of demyelinating neuropathy, with multi-organ involvement characterised by plasma cell dyscrasia and VEGF overproduction. No treatments have been established for patients with POEMS syndrome who are not eligible for stem-cell transplantation. Thalidomide suppresses VEGF and plasma cell proliferation. We aimed to assess the safety and efficacy of thalidomide for the treatment of POEMS syndrome.**

Methods **We did a randomised, double-blind, placebo-controlled, phase 2/3 trial at 12 hospitals in Japan. Adults (age ≥20 years) with POEMS syndrome who were ineligible for autotransplantation were randomly assigned (1:1) by a minimisation method to treatment with oral dexamethasone (12 mg/m² per day on the first 4 days of every 28-day cycle) plus either oral thalidomide (200 mg daily) or placebo for six cycles. All study personnel and patients were masked to treatment allocation. The primary endpoint was the reduction rate of serum VEGF concentrations at 24 weeks. Analysis was by intention to treat. This study is registered with the UMIN Clinical Trials Registry, UMIN000004179.**

Findings **Between Nov 11, 2010, and July 3, 2014, we randomly assigned 25 patients to receive either thalidomide (n=13) or placebo (n=12); one patient in the placebo group was excluded from analyses because of a protocol violation. The adjusted mean VEGF concentration reduction rate at 24 weeks was 0·39 (SD 0·34) in the thalidomide group compared with –0·02 (0·54) in the placebo group (adjusted mean difference 0·41, 95% CI 0·02–0·80; p=0·04). Mild sinus bradycardia was more frequent in the thalidomide group than in the placebo group (seven [54%] *vs* zero; p=0·006). Five patients had serious adverse events: three in the thalidomide group (transient cardiac arrest, heart failure, and dehydration) and two in the placebo group (ileus and fever). No deaths occurred during the randomised study. In the 48-week open-label study period (n=22), newly developed adverse events were sinus bradycardia (n=4), constipation (n=5), and mild sensory neuropathy (n=5). Two patients died in the open-label study; both patients were initially in the placebo group, and the cause of death was progression of the disease.**

Interpretation **Thalidomide reduces serum VEGF concentrations and represents a new treatment for patients with POEMS syndrome who are not eligible for stem-cell transplantation. Thalidomide treatment poses a risk of bradycardia; however, the benefits are likely to exceed the risk.**

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, also known as Crow-Fukase syndrome, is a rare cause of demyelinating polyneuropathy associated with multi-organ involvement, plasma cell dyscrasia, and VEGF overproduction.[1,2] The pathogenesis of POEMS syndrome is not fully understood; however, upregulated VEGF is assumed to play a major part by its strong action on vascular permeability and neovascularisation. VEGF overproduction is likely to cause many of the symptoms, including capillary leak syndrome (pleural effusion, ascites, and oedema), skin angioma, and presumably peripheral neuropathy. The prevalence of POEMS syndrome in Japan is estimated to be 0·3 per 100 000 people.[3] The prevalence of POEMS syndrome was originally thought to be higher in Japan than in other countries.[4,5] However, findings from recent case series from the USA (n=99),[6] France (n=25),[7] China (n=99),[8] and India (n=29)[9] suggest that POEMS syndrome is widely distributed.

Patients with POEMS syndrome develop disabling polyneuropathy and massive pleural effusion or ascites resulting in multiple organ failure.[2,10] In the 1980s, the mean survival time was 33 months in 34 patients who were mainly treated with corticosteroids.[4] Since the

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See **Comment** page 1104

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Research in context

Evidence before the study

We searched PubMed up to March 31, 2016, with the following terms without language restrictions: "POEMS syndrome", "Crow-Fukase syndrome", "Takatsuki disease", "clinical trial", and "treatment". We identified no randomised clinical trials for polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, only observational or open studies with alkylating drugs, thalidomide, lenalidomide, bortezomib, or autologous peripheral blood stem-cell transplantation.

Added value of this study

This is, to our knowledge, the first randomised, placebo-controlled clinical trial of the safety and efficacy of any kind of intervention for POEMS syndrome. In our study, we found a significant improvement in serum concentrations of VEGF, motor function, and some measures of quality of life in patients with POEMS syndrome treated with thalidomide compared with those who received placebo. Thalidomide should be considered as an effective treatment for patients with this disorder.

Implications of all the available evidence

There is an urgent need for treatments for patients with POEMS syndrome. Our findings show that thalidomide is a new treatment option for patients with POEMS syndrome who are not eligible for autologous transplantation.

1990s, the treatment strategy for POEMS syndrome has shifted to suppression of monoclonal plasma cell proliferation; therapeutic interventions used for multiple myeloma have also been used for POEMS syndrome.[2,10,11] Autologous peripheral blood stem-cell transplantation with high-dose chemotherapy can result in substantial clinical improvement and has been suggested as the first-line treatment for appropriate candidates.[11–13] However, transplantation is not indicated in about half of patients because they are older than 65 years or have organ failure. Such patients have been treated with immunomodulatory drugs such as thalidomide,[14] lenalidomide,[15] or low-dose alkylators.[16,17] No randomised controlled trials have been done, mainly because of the rarity and severity of the disorder.[2,10]

Thalidomide was initially developed as a sedative, but was withdrawn from the market because of its teratogenic effects. The drug has since been recognised as having antiangiogenic and anti-inflammatory cytokine properties, and has been used to treat erythema nodosum leprosum and multiple myeloma.[18] Findings from observational studies have suggested that thalidomide use in patients with POEMS syndrome decreases serum VEGF concentrations, improves or stabilises symptoms, and is safe for use in patients who are not eligible for autotransplantation.[14] No standard treatment guidelines exist for POEMS syndrome because of the scarcity of evidence-based clinical trial data. We therefore investigated the safety and efficacy of thalidomide in patients with POEMS syndrome who were not eligible for autotransplantation.

Methods

Study design and patients

For **the trial protocol** see http://opac.ll.chiba-u.jp/da/curator/100005/?lang=1

The POEMS Syndrome Thalidomide (J-POST) Trial was an investigator-led, phase 2/3, randomised, double-blind, placebo-controlled trial at 12 hospitals in Japan. The trial consisted of two periods: a 24-week, double-blind, randomised, comparative study followed by a 48-week, open-label safety study.

The trial protocol has been published elsewhere.[19] Briefly, adults (age ≥20 years) with probable or definite POEMS syndrome according to published diagnostic criteria[11] who were ineligible for autotransplantation during the study period and did not have substantial electrocardiographic abnormalities were eligible for inclusion. Ineligibility for transplantation was defined as age older than 65 years, organ failure (renal, respiratory, or cardiac), or patient refusal. Patients who had unstable disease or received oral or intravenous corticosteroids within 4 weeks of providing informed consent were excluded.

The study protocol was approved by the institutional review board of each hospital. Patients gave written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned (1:1) by a minimisation method to receive thalidomide plus dexamethasone or matching placebo plus dexamethasone. The allocation was generated by a computer program located at the registration centre.[20] The allocation coordinators at the registration centre enrolled patients and assigned them to the trial groups, but they had no involvement in the rest of the trial. Assignment was stratified by serum VEGF concentration (≤3000 pg/mL or >3000 pg/mL) and the presence of pleural effusion (yes or no). The placebo capsules were indistinguishable in appearance and taste from the thalidomide capsules. The trial drugs were supplied in numbered containers and were distributed to each hospital at the start of the trial under the responsibility of SaK. All study personnel and patients were masked to treatment group allocation.

Procedures

This 24-week, double-blind, randomised comparative study consisted of six 28-day cycles. Oral thalidomide or placebo were continuously given after a titration period, and oral dexamethasone was administered at a dose of 12 mg/m² per day on the first 4 days of every cycle. The