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Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome (Review)

Kuwabara S, Dispenzieri A, Arimura K, Misawa S, Nakaseko C

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[Intervention Review]

Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome

Satoshi Kuwabara[1], Angela Dispenzieri[2], Kimiyoshi Arimura[3], Sonoko Misawa[1], Chiaki Nakaseko[4]

[1]Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan. [2]Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA. [3]Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan. [4]Department of Hematology, Chiba University Hospital, Chiba, Japan

Contact address: Satoshi Kuwabara, Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-Ku, Chiba, Chiba, 260-8670, Japan. kuwabara-s@faculty.chiba-u.jp.

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ABSTRACT

Background

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating and axonal mixed neuropathy with monoclonal plasma cell proliferative disorder and multiorgan involvement. The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytomas, is likely to be responsible for most of the characteristic symptoms. POEMS syndrome is a potentially fatal disease, and patients' quality of life deteriorates because of progressive neuropathy, massive pleural effusion or ascites, or thromboembolic events. There is a need for efficacious therapy to improve prognosis. This is the first update of a review first published in 2008.

Objectives

To assess the effects of treatment for POEMS syndrome.

Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register (23 February 2012), CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012) and CINAHL Plus (January 1937 to February 2012) for all papers on POEMS syndrome

Selection criteria

We sought all randomized and quasi-randomized controlled trials, and non-randomized controlled studies. Since we discovered no such clinical trials, we assessed and summarized all retrospective case series including five or more patients in the 'Discussion' section.

Data collection and analysis

Two review authors independently reviewed and extracted details of all potentially relevant trials with any treatment for POEMS syndrome. We then collated and summarized information on the outcome.

Main results

We found no randomized or non-randomized prospective controlled trials of treatment for POEMS syndrome. We summarized the results of retrospective case series containing five or more patients in the 'Discussion' section.

Authors' conclusions

There are no randomized or quasi-randomized controlled clinical trials of treatment for POEMS syndrome on which to base practice.

PLAIN LANGUAGE SUMMARY

Treatment for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)

POEMS syndrome is a rare disorder of the blood which can cause a polyneuropathy (nerve symptoms such as numbness, tingling, pain, and muscle weakness) but can also involve many of the organs of the body, causing enlarged organs or organomegaly (usually liver, spleen, and lymph nodes), changes in hormone production or endocrinopathy (gynecomastia in men), abnormal blood protein (M-protein), and skin changes such as increased pigmentation or skin thickening. Its cause is not known. The quality of life of people with POEMS deteriorates because of progressive neuropathy, and accumulation of fluid in the limbs or in the abdominal cavity or cavity around the lungs. It is a potentially fatal disease, and serious complications can arise due to multiorgan failure. There is no established treatment regimen, but potentially effective treatments that have been tried include chemotherapy, irradiation, corticosteroids, thalidomide or lenalidomide, and blood stem cell transplantation. This review found no randomized controlled trials of treatments for POEMS syndrome. Prospective treatment trials are needed to establish the relative values of different treatments.

BACKGROUND

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating and axonal mixed neuropathy with monoclonal plasma cell proliferation and multiorgan involvement (Bardwick 1980; Nakanishi 1984). Skin changes include angiomata, skin thickening, pigmentation, and hypertrichosis. Important clinical features other than the five cardinal symptoms of POEMS include peripheral edema, pleural effusion, ascites, sclerotic bone lesions, Castleman disease, papilledema, polycythemia, and thrombocytosis. POEMS syndrome has also been called Crow-Fukase syndrome, Takatsuki syndrome, and PEP (plasma cell dyscrasia, edema, and pigmentation) syndrome. The prevalence of POEMS syndrome is unclear, but a recent national survey conducted in Japan showed a prevalence of approximately 0.3 per 100,000 (Arimura 2007). The disease was initially thought to be more common in Japan given that the largest initial reports were from Japan (Takatsuki 1983; Nakanishi 1984). However, large series have also been reported from France (Soubrier 1994), the United States (Dispenzieri 2003; Allam 2008), China (Cui 2011; Li 2011b), and India (Kulkarni 2011), and the disorder has been increasingly recognized in many areas of the world.

The neuropathy is a symmetric sensory-motor polyneuropathy, predominantly affecting the distal lower limbs. Neuropathologically, a mixture of demyelination and axonal degeneration is usually present. Uncompacted myelin lamellae are found in most cases, and have been suggested to be highly characteristic of this syndrome (Vital 2003). Segmental demyelination, particularly in the proximal nerve segments, endoneurial edema, and involvement of endoneurial vessels are also frequently seen (Koike 2000; Scarlato 2005). POEMS syndrome is frequently mistaken for chronic inflammatory demyelinating polyneuropathy (CIDP) because both disorders show peripheral nerve demyelination (Sung 2002; Mauermann 2012; Nasu 2012). It is necessary to recognize POEMS syndrome as a cause of demyelinating neuropathy, and the differentiation from CIDP is clinically very important because fundamentally different treatments are required for each disease (Dispenzieri 2011; Kuwabara 2011).

POEMS syndrome is a potentially fatal disease, and patients' quality of life deteriorates because of progressive neuropathy (Isose 2011), massive peripheral edema, pleural effusion, or ascites. Serious complications such as multiorgan failure from capillary leak syndrome, restrictive lung disease, pulmonary hypertension (Allam 2008), and thromboembolic events may occur, contributing to the poor prognosis. In a retrospective series involving 102 Japanese patients in the 1980s, most of whom were treated with corticosteroids without chemotherapy, follow-up data were available in 58 patients. Thirty-eight of them died, with a mean survival period of 33 months (Nakanishi 1984). In another retrospective study conducted in the United States, more intensive treatments were administered; out of 99 patients, 65 were treated with irradiation to a local osteosclerotic lesion and 48 with melphalan and prednisone. Overall median survival was 165 months, but patients with edema, effusion, or ascites had a mean survival of 79 months, and patients with fingernail clubbing had a mean survival of 31 months (Dispenzieri 2003). In a report from Italy, 6 of 11 patients died 3 to 23 months after combined treatment with corticosteroids, alkylating agents, and/or plasma exchange (Scarlato 2005). In one French study, at least 7 out of 15 patients were alive for more than five years (Soubrier 1994).

The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytomas (Nakajima 2007), is likely to be responsible for most of the characteristic symptoms (Watanabe 1996; Soubrier 1999). Almost all patients with POEMS syndrome have highly elevated serum VEGF levels, and disease activity appears to correlate with VEGF levels (Watanabe 1998; Hashiguchi 2000; D'Souza 2011). VEGF is a potent multifunctional cytokine that induces prominent angiogenesis and microvascular hyperpermeability, and therefore could cause many of the symptoms of POEMS syndrome.

There are no randomized controlled trials (RCTs) for POEMS syndrome, presumably because of the rarity of the disorder, and therefore no established treatment regimen. Previous case reports and series have described patients with POEMS syndrome who have been treated with irradiation, resection of plasmacytomas, chemotherapies, corticosteroids, plasmapheresis, and intravenous immunoglobulin infusion. Irradiation has usually been proposed for patients with a solitary plasmacytoma. If patients have wide spread osteosclerotic lesions, systemic chemotherapy is necessary (Kuwabara 1997; Dispenzieri 2005a; Dispenzieri 2005b). In appropriate candidates, high-dose chemotherapy with autologous peripheral blood stem cell transplantation (auto-PBSCT) is recommended (Jaccard 2002; Dispenzieri 2004; Kuwabara 2006). This treatment resulted in obvious improvement in neuropathy as well as other symptoms, with a significant decrease in serum VEGF levels (Kuwabara 2008a; D'Souza 2011). From data of published experience, the transplant-related mortality was initially reported to be 7.4% (Dispenzieri 2005a), but an update in 2008 suggested a lower transplant-related mortality (3.3%) with better peri-transplant supportive care (Dispenzieri 2008). Indications for this treatment have not yet been established, and long-term prognosis is unclear. Treatments that may be considered in the future include lenalidomide or thalidomide, anti-VEGF monoclonal antibody (bevacizumab), and bortezomib.

No RCTs for POEMS syndrome had been published when the protocol for this review was written in 2008 or at the time of this update in 2012. This review attempts to systematically consider the available evidence and highlights the need for clinical trials and prospective data collection in POEMS syndrome. It should serve as a basis for maintaining an up-to-date record.

OBJECTIVES

To assess the effects of treatment for POEMS syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all RCTs or quasi-RCTs (alternate or other systematic treatment allocation). It was anticipated that this type of evidence would not be available, and therefore we also sought non-randomized trials. We planned to report historically controlled trials and trials with concurrent controls, provided adequate diagnostic criteria were applied, and adequate descriptions of interventions and clinical courses were stated.

Given the anticipated lack of studies that included pre-planned data collection and eligibility criteria, and in an attempt to summarize the available clinical data, we have reviewed other types of studies and summarized them in the Discussion. We have included comparative cohort studies, case-control studies and case series of at least five participants in this assessment.

Types of participants

Eligible studies had to include participants of any age with POEMS syndrome. The clinical manifestations should not be explained by other neurological or haematological disease, including neuropathy associated with systemic vasculitis, neuropathy associated with anti-MAG (myelin-associated glycoprotein) antibody, and multiple myeloma. Appropriate clinical and laboratory investigations should have been performed to exclude other recognized causes of the neuropathy (Dispenzieri 2005a; Dispenzieri 2011).

It is recognized that not all five features of 'POEMS' are required to make the diagnosis of POEMS syndrome (Dispenzieri 2003), and that an elevated serum VEGF level is a diagnostic marker (Watanabe 1996). However, measurements of serum VEGF were not widely available until 2000, and many earlier reports were missing this information. This review will include patients as having definite or probable POEMS syndrome using the following diagnostic criteria modified from Dispenzieri 2005a and Dispenzieri 2007a.

Criteria for the diagnosis of POEMS syndrome

Major criteria

(a) Polyneuropathy (mandatory)
(b) Monoclonal plasma cell proliferative disorder (mandatory)*
(c) Elevation of serum or plasma VEGF levels
(d) Sclerotic bone lesions
(e) Castleman disease**

Minor criteria

(f) Organomegaly (hepatosplenomegaly or lymphadenopathy)
(g) Edema (edema, pleural effusion, or ascites)
(h) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, or pancreatic)***
(i) Skin changes (hyperpigmentation, hypertrichosis, plethora, cyanosis, hemangiomata, or white nails)
(j) Papilledema
(k)Thrombocytosis and/or polycythemia

(1) Definite POEMS syndrome: three major criteria and at least one minor criterion.
(2) Probable POEMS syndrome: two major criteria, with at least one minor criterion.

* Defined by M-protein, or monoclonal plasma cell proliferation in bone marrow biopsy or biopsy of a plasmacytoma or sclerotic lesion.

** There is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal plasma cell disorder that is not accounted for in this list. This entity should be considered separately.

***Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

Types of interventions

We considered all interventions. We had anticipated that most studies would focus on the use of focal irradiation, corticosteroids, alkylating agent-based chemotherapy, high-dose chemotherapy with auto-PBSCT, lenalidomide or thalidomide, bevacizumab (anti-VEGF monoclonal antibody), bortezomib, or combinations of these treatments. We considered studies that have compared one treatment with another or against placebo. We have also assessed series that have reported outcomes in patients not receiving any of the above treatments in the Discussion.

Types of outcome measures

Primary outcomes

Survival two years after initiation of treatment.

Secondary outcomes

The secondary outcome measures include improvement in disability as defined by the original authors at least one year after the start of treatment. Where possible, we planned to transform disability data to the Overall Neuropathy Limitations Scale (ONLS) (Graham 2006). We defined improvement as at least one grade decrease on this scale. We considered unchanged or increased grades on the scale as no improvement:

Arm grade
"0 = Normal" to "5 = Disability in both arms preventing all purposeful movement".
Leg grade
"0 = Normal" to "7 = Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs".

Assessment of manifestations of disease was also evaluated one year after the start of treatment.

1. Improvement by one or more ONLS grades.
2. Disappearance of extravascular volume overload (edema, pleural effusion, and ascites).
3. Normalization of serum VEGF levels.
4. Disappearance of M-protein.
5. Adverse effects attributable to treatment, which require or prolong hospitalization, including treatment-related death.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Disease Group Specialized Register (23 February 2012) using the following search terms: "POEMS syndrome", its synonyms "Crow-Fukase syndrome", "Takatsuki syndrome", and "PEP (plasma cell dyscrasia, edema, and pigmentation) syndrome", and "paraproteinemia". We adapted this strategy to search for all papers on POEMS syndrome in CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012) and CINAHL Plus (January 1937 to February 2012). The detailed search strategies are in the appendices: Appendix 1 (MEDLINE), Appendix 2 (EMBASE), Appendix 3 (CINAHL Plus) and Appendix 4 (CENTRAL).

Searching other resources

We reviewed the bibliographies of the trials and studies identified, contacted the authors and known experts in the field, and

approached pharmaceutical companies to identify additional published or unpublished data

Data collection and analysis

Selection of studies

Two authors (SK and AD) independently reviewed titles and abstracts from literature searches to identify potentially relevant trials for full review. A considerable proportion of the literature was in Japanese journals. CN and SM assessed Japanese articles. From the full text, we planned to select trials that met the selection criteria for inclusion and grade their methodological quality. Disagreement did not occur but we would have resolved it by consensus with third party adjudication (AK).

Assessment of risk of bias of included studies

The 'Risk of bias' assessment for included studies was to take into account allocation concealment, security of randomization, incomplete outcome data (intention-to-treat analysis), selective reporting, patient blinding, observer blinding, and other sources of bias (Higgins 2011). We also planned to assess whether the studies had explicit inclusion and exclusion criteria, and how studies dealt with baseline differences between the experimental groups . We planned to use assessments of 'High risk of bias', 'Low risk of bias' or 'Uncertain risk of bias'. We planned to resolve disagreement by consensus, with third party adjudication if necessary.

Statistical analysis

We would have calculated risk ratios (RRs) from dichotomized proportional data for each study with the Cochrane Review Manager (RevMan) software. We would have calculated the pooled RR estimate to assess the overall efficacy of the studies. Where studies used survival data analysis, such as Cox regression producing results in the form of hazard ratios, we would have combined them using the RevMan generic inverse variance (GIV) facility. We would have calculated mean differences (MD) from the mean changes in disability scores for each study. We would have derived standard deviations (SDs) for each study by calculation or extraction from the available data. If necessary, we would have contacted authors for the original data.

For all analyses, we would have determined 95% confidence intervals (CIs). We would have performed a sensitivity analysis on the basis of methodological quality of the studies. We would have carried out separate sensitivity analyses according to the presence or absence of individual internal validity items, and for each level of allocation concealment of treatment. In the Discussion, we use information from observational studies and other sources to describe side effects and costs likely to be associated with the immunosuppressive regimens considered in the review.

RESULTS

Description of studies

Results of the search

The number of papers found by the new, current strategies were Cochrane Neuromuscular Disease Group Specialized Register 1, MEDLINE 736, EMBASE 770, and CENTRAL 0.

We found no RCTs, quasi-RCTs, historically controlled trials, or trials with concurrent controls that met the selection criteria. We have summarized, in the Discussion, case series containing at least five participants in which sufficient clinical features were available; reasonable descriptions of interventions were given; and enough information was available to assess one or more of our pre-defined clinical outcomes.

Risk of bias in included studies

Not applicable.

Effects of interventions

We found no RCTs of any treatment in POEMS syndrome, nor did we find any prospective cohort series or case control studies. A number of series met our criteria for discussion, which we have summarized below.

DISCUSSION

The literature on treatment for POEMS syndrome is characterized by a large number of case reports and small retrospective case series. Additional complexity is created by the fact that we do not yet have an accurate picture of the natural history of the disorder. However, a retrospective series involving 102 Japanese patients in the 1980s, most of whom were treated with only corticosteroids, showed that of 58 patients with available follow-up data, 38 died with a mean survival period of 33 months (Nakanishi 1984). These data suggest that mortality is high without appropriate treatment. Even though peripheral neuropathy can lead to substantial disability and the disorder is potentially fatal due to multi-system failure (Kuwabara 1997; Scarlato 2005), no RCTs or quasi-RCTs for POEMS syndrome have been published. In the absence of evidence from RCTs on treatment for POEMS syndrome, the choice of treatment must be guided by experience in observational studies.

Summary of nonrandomised studies including more than five participants

We have summarized the data from retrospective series including five or more patients in Table 1. The search strategy identified 10 such studies as outlined below (Kuwabara 1997; Jaccard 2002; Dispenzieri 2003; Dispenzieri 2004; Kuwabara 2006; Dispenzieri 2008; Kuwabara 2008a; Kuwabara 2008b; Jimenez-Zepeda 2011; Li 2011a). Two retrospective studies compared the effects of corticosteroid and melphalan chemotherapy (Kuwabara 1997) or melphalan and auto-PBSCT (Kuwabara 2006). One study assessed the value of radiation therapy (Dispenzieri 2003). Other studies included patients treated with high-dose chemotherapy with auto-PBSCT (Jaccard 2002; Dispenzieri 2004; Dispenzieri 2008; Kuwabara 2008a; Jimenez-Zepeda 2011) or corticosteroids (Li 2011a). The final study assessed the effects of thalidomide (Kuwabara 2008b).

Melphalan, corticosteroids, and radiation

In a retrospective study of 12 Japanese patients with POEMS syndrome, six were treated with long-term melphalan chemotherapy between 1990 and 1995, and the remaining six, who had been treated with corticosteroid alone in the 1980s, served as historical controls. The prognosis in the corticosteroid group was markedly poor; five of the six died from 9 to 61 months (mean 28 months) after the start of treatment. Patients treated with melphalan had better outcomes; five of them survived the follow-up period (29 to 64 months), and one died 50 months

after treatment. Any neurological improvement was slow and incomplete (Kuwabara 1997). The two-year survival rate for those patients receiving corticosteroid alone was 33% versus 100% for those receiving melphalan therapy.

In a retrospective study of 99 American patients with POEMS, 64 patients were treated with 70 courses of radiation, 48 with melphalan and prednisone, 15 with combination chemotherapy including cyclophosphamide, 41 with prednisone or dexamethasone alone, 30 with plasmapheresis, and nine with intravenous immunoglobulin (Dispenzieri 2003). In this series, patients with a solitary plasmacytoma received radiation therapy, and those with multiple or no detectable osteoclastic lesions had systemic treatment. Two-year survival for the patients who received radiation was approximately 90%, versus approximately 78% for those who received any form of systemic therapy.

Autologous peripheral blood stem cell transplantation (auto-PBSCT)

Since about the year 2000, many case reports or case series have demonstrated dramatic effects of auto-PBSCT. In a study of five French participants with POEMS syndrome who received auto-PBSCT, all five patients showed marked improvement in neurological symptoms, and other manifestations of the syndrome, and clinical remission persisted during the follow-up periods of 12 to 58 months (Jaccard 2002). The two-year survival rate was 4/4 (100%).

Another study in the USA described efficacy of auto-PBSCT in 16 patients; 14 showed substantial neurological improvement or stabilization, and other features of the syndrome improved substantially. At the time of the publication of the results of the study, there was one patient who had not yet returned for his post-transplant evaluation and there was one transplant-related death. Peri-transplant morbidity was significant, with five patients requiring intubation for respiratory compromise (Dispenzieri 2004). In a follow-up study, the same research group expanded their experience to 30 patients, and reported that a corticosteroid-responsive engraftment syndrome was common in POEMS patients undergoing auto-PBSCT (Dispenzieri 2008). Early recognition of this syndrome with early institution of high-dose corticosteroids significantly reduced the transplant-related morbidity (Jimenez-Zepeda 2011). As before, patients showed excellent clinical responses along with reductions of plasma VEGF levels. The estimated two-year overall survival was over 95%.

Another study in Japan compared effects of auto-PBSCT (n = 4) and conventional melphalan chemotherapy (n = 8) by monitoring serum VEGF levels. In four patients treated with auto-PBSCT, there was a dramatic improvement in neurological and other symptoms, with rapid normalization of serum VEGF levels. Clinical remission persisted during a follow-up period ranging from 12 to 18 months. Among eight patients treated with conventional chemotherapy, neurological symptoms gradually lessened over 12 to 24 months in four but did not significantly change in the remaining four. Moreover, two patients died seven and nine years after the initiation of melphalan therapy: one with a myelodysplastic syndrome secondary to melphalan administration and the other of massive intracerebral hemorrhage (Kuwabara 2006). Later, the same investigators showed, in nine patients, detailed changes in neurological scaling, nerve conduction study results, and serum VEGF levels, all of which showed significant improvement after auto-PBSCT (Kuwabara 2008a).

Thalidomide

One study described the efficacy of thalidomide in nine Japanese patients. During follow-up periods of 8 to 23 months (mean, 15 months), all patients showed substantial clinical improvement (n = 6) or stabilization of symptoms (n = 3). Serum VEGF levels decreased in all and were normalized in five. Nerve conduction velocities in the median nerve increased in seven. There were no serious adverse effects, including no reports of a thalidomide neuropathy (Kuwabara 2008b).

Nonrandomised studies including less than five participants

Treatments that may be considered in the future include lenalidomide, and anti-VEGF monoclonal antibody (bevacizumab). Like thalidomide (Sinisalo 2004; Kim 2006; Kuwabara 2008b), lenalidomide (Dispenzieri 2007b) has anti-angiogenic, anti-inflammatory, and immunomodulating action. Lenalidomide and thalidomide have been successfully used in treatment of POEMS syndrome, but so far there are only limited data. Compared with thalidomide, which can induce peripheral neuropathy as an adverse effect, lenalidomide has a much lower risk of peripheral neuropathy and should be considered in future studies. Five case reports have demonstrated successful treatment with bortezomib, a proteasome inhibitor (Tang 2009; Yuan 2009; Kaygusuz 2010; Sobas 2010; Ohguchi 2011). Bevacizumab has been tried with mixed results: among a total of five patients who were treated with bevacizumab, three patients had benefit, but two died (Badros 2005; Straume 2006; Kanai 2007; Ohwada 2009).

Disease types (solitary or diffuse disease) and rationale for treatment

Overproduction of VEGF, presumably secreted by monoclonal plasma cells, is considered to play an important role in the pathogenesis of POEMS syndrome. Therefore, the target for treatment of POEMS syndrome should be proliferative plasma cells, or VEGF. So far, for patients with a solitary plasmacytoma (usually an osteosclerotic bone lesion), irradiation, or surgical resection has usually been proposed. If patients have widespread osteosclerotic lesions or no detectable bone lesion, systemic chemotherapy is recommended (Dispenzieri 2007a; Dispenzieri 2011). Melphalan has been most frequently used as a chemotherapeutic agent for the treatment of POEMS syndrome. A recent prospective study of treatment with melphalan in combination with dexamethasone reported high efficacy and low toxicity (Li 2011a). However, limitations of this drug include a high rate of relapse (Kuwabara 2006) and secondary myelodysplastic syndrome or acute leukemia (Dispenzieri 2007a). Recent case series and case reports have shown that high-dose chemotherapy with autologous peripheral blood stem cell support is efficacious treatment for POEMS syndrome. This treatment leads to obvious improvement in peripheral neuropathy as well as other symptoms, and a significant decrease in serum VEGF levels. However, transplantation is not indicated for elderly patients (usually older than 65 years) and patients with significant organ involvement such as renal failure. If the published experience of auto-PBSCT is pooled, the mortality figure is estimated to be 3/112 (2.7%), and the number appears similar to the two per cent transplant-related mortality in patients

with multiple myeloma. Long-term outcomes of patients treated with auto-PBSCT have not yet been elucidated and should be carefully monitored. So far, five case reports of patients with relapse three to seven years after auto-PBSCT have been published (Giglia 2007; Samaras 2007; Dispenzieri 2008; Imai 2009; Mahdi-Rogers 2009).

Despite the absence of evidence from RCTs, the review authors consider that the foundation of treatment for patients with a solitary osteosclerotic lesion and who do not have clonal plasma cells on iliac crest biopsy should be local irradiation. For patients under 65 years with diffuse disease, as demonstrated by multiple bone lesions or documented clonal plasma cells in iliac crest biopsy, high-dose melphalan with auto-PBSCT is appropriate. Lenalidomide or thalidomide, anti-VEGF monoclonal antibody, and conventional chemotherapy with melphalan or cyclophosphamide may also be treatment options but there are fewer data to support the use of these therapeutic options. Evidence-based data on which to base treatment decisions for POEMS syndrome are of importance, but because of the rarity of the disorder, phase II and III trials have not been done. A higher awareness of the syndrome may demonstrate that its prevalence is higher than previously thought, making prospective clinical trials feasible.

AUTHORS' CONCLUSIONS

Implications for practice

There are no RCTs of treatment for POEMS syndrome on which to base practice.

Implications for research

Prospective treatment trials are needed to establish the relative values of treatments for POEMS syndrome. Radiation, alkylator based therapy, and novel agents may all play a role. For selected patients, high-dose chemotherapy with autologous peripheral blood stem cell transplantation appears to be effective and potentially associated with a lower risk of myelodysplastic syndrome than conventional alkylator therapy; however, until the pathogenesis of the disease is fully understood and until prospective clinical trials are conducted, treatment decisions will be based on anecdotal experience.

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ADDITIONAL TABLES

Table 1. Data from series of five or more patients

Study ID/ Name	Treatment	N	2-year survival	1-year remission	1-year no edema	1-year normal VEGF	Adverse event
Kuwabara 1997	Corticosteroid	6	2 (33%)	3 (50%)	3 (50%)	-	-
	Melphalan	6	6 (100%)	4 (67%)	6 (100%)	-	2 leukocytopenia
Jaccard 2002	Transplantation	5	4/4 (100%)	5 (100%)	5 (100%)	2/2 (100%)	-
Dispenzieri 2003	Radiation	64	90%	-	-	-	-
	Melphalan	48	78%	-	-	-	-
Dispenzieri 2004	Transplantation	16	15 (94%)	14 (87%)	11/14 (79%)	-	1 transplant-related death, 5 respiratory failure
Kuwabara 2006	Melphalan	8	8 (100%)	4 (50%)	4/8 (50%)	2/8 (25%)	2 leukocytopenia
	Transplantation	4	4 (100%)	4 (100%)	4 (100%)	4 (100%)	-
Dispenzieri 2008	Transplantation	30[a]	29 (97%)	-	-	-	15 engraftment syndrome
Kuwabara 2008a	Transplantation	9[b]	6/6 (100%)	9 (100%)	9 (100%)	9 (100%)	1 respiratory failure
Kuwabara 2008b	Thalidomide	9	3/3 (100%)	5 (56%)	7 (78%)	5 (56%)	3 skin eruption
Jimenez-Zepeda 2011	Transplantation	8	100%	-	-	-	-
Li 2011a	Melphalan/dexamethasone	31	13/13 (100%)	31/31 (100%)	-	23/24 (96%)	4 hematologic toxicity 2 bacterial pneumonia

a Includes 11 of 16 patients in Dispenzieri 2004.
b Includes 4 patients in Kuwabara 2006.

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 clinical trials as topic.sh.
6 randomly.ab.
7 trial.ti.
8 or/1-7
9 (animals not (animals and humans)).sh.
10 8 not 9
11 Paraproteinemias/ or paraproteinemia.mp.
12 POEMS Syndrome/
13 POEMS syndrome.mp.
14 crow-fukase syndrome.mp.
15 takatsuki syndrome.mp.
16 PEP syndrome.mp.
17 plasma cell dyscracia.mp.
18 osteosclerotic myeloma.mp.
19 (Polyneuropathy and Organomegaly and Endocrinopathy and Edema and M-protein and skin abnormalities).mp.
20 or/11-19
21 10 and 20

Strategy without filter

1 POEMS Syndrome/
2 POEMS syndrome.mp.
3 (crow-fukase adj6 syndrome$1).mp.
4 ((takatsuki adj6 syndrome$1) or (takatsuki adj3 disease)).mp.
5 PEP syndrome.mp.
6 plasma cell dyscracia.mp.
7 (Polyneuropathy and Organomegaly and Endocrinopathy and Edema and M-protein).mp.
8 or/1-7

Appendix 2. EMBASE (OvidSP) search strategy

1 crossover-procedure/
2 double-blind procedure/
3 randomized controlled trial/
4 single-blind procedure/
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
6 or/1-5
7 human/
8 6 and 7
9 nonhuman/ or human/
10 6 not 9
11 8 or 10
12 Paraproteinemia/
13 paraproteinemia.mp.
14 POEMS syndrome.mp.
15 crow-fukase syndrome.mp.
16 Crow Fukase Syndrome/
17 takatsuki syndrome.mp.
18 PEP syndrome.mp.
19 plasma cell dyscracia.mp.
20 osteosclerotic myeloma.mp.
21 (Polyneuropathy and Organomegaly and Endocrinopathy and Edema and M-protein and Skin abnormalities).mp.
22 or/12-21

23 11 and 22

Strategy without filter

1 POEMS syndrome/
2 POEMS syndrome.mp.
3 Crow Fukase Syndrome/
4 (crow-fukase adj6 syndrome$1).mp.
5 ((takatsuki adj6 syndrome$1) or (takatsuki adj3 disease)).mp.
6 PEP syndrome.mp.
7 plasma cell dyscracia.mp.
8 (Polyneuropathy and Organomegaly and Endocrinopathy and Edema and M-protein).mp.
9 or/1-8

Appendix 3. CINAHL Plus (EBSCOhost) search strategy

S23 S18 and S22
S22 S19 or S20 or S21
S21 "crow-fukase syndrome"
S20 ("POEMS Syndrome") or (MH "POEMS Syndrome")
S19 ("paraproteinemia") or (MH "Paraproteinemias")
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 Search modes - Boolean/Phrase
S17 ABAB design* y
S16 TI random* or AB random*
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or
dummy))
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment*

or preventive or therapeutic)) and (TI (trial*) or AB (trial*))
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or
systematic review*))
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*))
S11 PT ("clinical trial" or "systematic review")
S10 (MH "Factorial Design")
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")
S8 (MH "Meta Analysis")
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")
S6 (MH "Quasi-Experimental Studies")
S5 (MH "Placebos")
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")
S3 (MH "Clinical Trials+")
S2 (MH "Crossover Design")
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random
Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random
Sample")

Strategy without filter

S8 S1 or S2 or S6
S7 S1 or S2 or S3 or S4 or S5 or S6
S6 Polyneuropathy Organomegaly Endocrinopathy
S5 plasma cell dyscracia
S4 PEP syndrome
S3 ((takatsuki syndrome) or (takatsuki disease))
S2 "crow-fukase syndrome"
S1 ("POEMS Syndrome") or (MH "POEMS Syndrome")

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor Paraproteinemias, this term only
#2 Paraproteinemias
#3 POEMS Syndrome

#4 MeSH descriptor POEMS Syndrome explode all trees
#5 crow-fukase syndrome
#6 takatsuki syndrome
#7 PEP syndrome
#8 plasma cell dyscracia
#9 osteosclerotic myeloma
10(Polyneuropathy and Organomegaly and Endocrinopathy and Edema and M-protein and skin abnormalities)
11(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
12(#11)

WHAT'S NEW

Date	Event	Description
16 January 2012	New citation required but conclusions have not changed	No change to conclusions. Text updated throughout
17 December 2011	New search has been performed	Searches updated to February 2012. No RCTs identified but two non-randomised studies added to the Discussion. Methods re-vised to reflect updated Cochrane 'Risk of bias' methodology

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 4, 2008

Date	Event	Description
15 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Satoshi Kuwabara and Angela Dispenzieri wrote the review, which was critically reviewed and amended by Sonoko Misawa, Kimiyoshi Arimura, and Chiaki Nakaseko.

DECLARATIONS OF INTEREST

Chiaki Nakaseko, Satoshi Kuwabara, Kimiyoshi Arimura, Sonoko Misawa: none known

Angela Dispenzieri: grants paid to her institution for clinical trials (Celgene, Johnson & Johnson) or to discuss future protocols (Onyx, Millenium). She has received financial support for travel to deliver a lecture from Binding Site. She states that none of these interactions affect the content of the present review.

SOURCES OF SUPPORT

Internal sources

- Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan.
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- Department of Neurology and Geriatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the methods section to reflect updated Cochrane 'Risk of bias' methodology.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Hematopoietic Stem Cell Transplantation [methods]; Melphalan [therapeutic use]; POEMS Syndrome [*therapy]; Retrospective Studies; Thalidomide [therapeutic use]

MeSH check words

Humans