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Amyloidosis and POEMS Syndrome

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Abstract

Importance of the field—Treatment options for amyloidosis and POEMS have rapidly increased in the past years, but many patients are diagnosed late in the disease course and do not receive state of the art therapy

Areas covered in this review—Stem cell transplantation and novel agents have widened the chemotherapy alternatives available in these disorders and combinations of novel agents with high dose therapy further improve treatment options. This review covers the main areas of debate in the optimal treatment amyloidosis and POEMS patients, focusing on the implications for everyday clinical practice and management strategies published in the past 36 months.

What the reader will gain—Insights into treatment strategies are provided in the review. Keys to early recognition of the syndromes are reviewed

Take home message—With early diagnosis most patients are therapy candidates. New agents and new application of stem cell transplantation have dramatically improved outcomes for these previously uniformly poor prognosis disorders.

Keywords

amyloidosis; POEMS syndrome; osteosclerotic multiple myeloma; bortezomib; lenalidomide; thalidomide; stem cell transplantation; multiple myeloma; Castleman's Disease; monoclonal gammopathy of undetermined significance; paraneoplastic syndrome; vascular endothelial growth factor

Amyloidosis

1.Introduction

Both immunoglobulin light chain amyloidosis and POEMS syndrome are associated with an underlying plasma cell dyscrasia ¹. The current understanding of the pathology of the disorder are that clonal plasma cells synthesize immunoglobulin light chain or heavy chain fragments ² that cannot be completely broken down to constituent amino acids and undergo misfolding that makes the peptide resistant to catabolic enzymes ³. The subunits of the immunoglobulin protein can range from 6 to 20 kDa and represent the amyloid fibril subunit monomer. These monomers assemble into protofibrils, which wind to form the amyloid fibril, which with x-ray defraction microscopy demonstrates a β -pleated sheet. This fibril binds Congo red and exhibits green birefringence under polarized light ⁴. The organ dysfunction seen in patients with

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Declaration of interest

A Dispenzieri; Celgene: has received dollars for trial research and honoraria for speaking engagements. Binding Site, UK: honoraria for speaking engagements. M A Gertz has worked with Amgen, Eisai, Celgene and Genzyme.

amyloidosis may not be related to the deposition of the fully formed fibril. Soluble toxic intermediates may mediate the dysfunction of visceral organs. The Congo red positive fibril may be a marker but not the cause of the problem ⁵.

There are two ways to attempt to manage amyloidosis. One would be to interfere with misfolding of the amyloid fibril rendering it soluble. Although research efforts are underway to manage TTR amyloid in this fashion, there are no active studies that are attempting to solubilize immunoglobulin light chain amyloid ⁶. The second option is to use cytotoxic chemotherapy to destroy the clonal plasma cells, which are the source of the immunoglobulin light chain that deposits as the intact amyloid fibril ⁷. Amyloidosis specific scanning also has demonstrated regression of deposits following chemotherapy ⁸. Much of the pharmacologic information on the treatment of amyloidosis is derived from the larger population of patients with multiple myeloma, and it is subsequently applied to patients with amyloidosis.

2. Alkylator-Based Therapy

The standard of care for the treatment of amyloidosis was melphalan and prednisone given orally for 4 to 7 days every 4 to 6 weeks ^{9,10}. The disadvantages of these treatments include low response rates in the range of 15 to 20% and a prolonged time to response. Rapid response is desirable in order to prevent progressive organ damage while waiting for chemotherapy to reduce the toxic light chain production. Long-term, melphalan exposure increases the risk of treatment-induced leukemia or myelodysplasia ¹¹. One advantage of melphalan-prednisone is that it can be administered to virtually any patient regardless of age, performance status, and serum creatinine. Given the potential benefits, there is little reason not to consider a trial of melphalan-prednisone if other alternatives are not suitable ¹².

The use of melphalan with high-dose dexamethasone instead of prednisone has been reported in the management of amyloidosis. In the original study, patients were selected on the basis of their ineligibility for high-dose melphalan plus transplant therapy. Of 46 patients, a hematologic response was seen in 31, and a hematologic complete response was seen in 15 (33%). Improvement in organ dysfunction was seen in 22 patients (48%). The 100-day mortality was 4%, resolution of cardiac failure was seen in 6 of 32 patients with a median time to response of 4.5 months, and only 11% adverse effects ¹³.

At 5-year follow-up, the actuarial survival was approximately 50%, and the progression-free survival was 40%. Patients who relapsed could be successfully re-induced with melphalan and dexamethasone. Of 41 evaluable patients, there were ultimately 30 responders and 11 nonresponders with the responders median survival not reached and nonresponders median survival just over 2 years ¹⁴. In an extended patient population of 126 consecutive patients, hematologic response was seen in 62% with 26% complete responses. The median time to response was 3.5 months; 33% achieved an organ response. The median progression-free survival was 2.5 years; and on multivariate analysis for survival, only NT-pro-BNP was independently associated with overall and progression-free survival. Hematologic response improved overall survival and progression-free survival, and complete responders did better than partial responders. The longest overall survival was obtained in patients who had a reduction in NT-pro-BNP. The estimated overall survival at three years was 94% in patients with both NT-pro-BNP and free light chain reductions ¹⁵.

Boston University Medical Center has used pulse low-dose melphalan in patients ineligible for stem cell transplant because of severe cardiac involvement or poor performance status. All patients received growth factor support and the melphalan dose was adjusted to produce mid-cycle myelosuppression. Fifteen patients, median age 55, received a median of three cycles. Eight of 10 evaluable patients had a hematologic response; 2 of 8 were complete. The median survival was 2 months. Ten patients died within 5 weeks of starting treatment ¹⁶. A report of

48 evaluable patients from the same center who were ineligible for stem cell transplantation primarily because of severe cardiac involvement achieved a complete hematologic response rate of 15% and the median survival of 70 patients had not been reached with a 60% overall survival at 3 years¹⁷. Melphalan and dexamethasone have replaced melphalan and prednisone as the standard of care in patients who are not transplant eligible.

3. Stem Cell Transplantation

The first phase II trials using dose-intensive melphalan with autologous hematopoietic stem cell replacement were first reported 14 years ago^{18,19}. Hematopoietic stem cell transplantation was reported to produce hematologic responses in nearly two-thirds of patients. Validation of the organ responses using amyloid P-component scanning has been performed. Quality of life following stem cell transplantation is improved²⁰. In carefully selected patients, the therapy is applicable to those over the age of 65 years²¹. The best outcomes following stem cell transplantation are in those patients who achieve a complete hematologic response. Amyloid-related organ disease improves in the majority of patients who achieve a complete hematologic response after high-dose therapy²². Determinants of outcome following stem cell transplantation include posttransplantation development of acute renal insufficiency²³, early lymphocyte recovery²⁴, the development of excessive fluid accumulation during mobilization²⁵, and the pretransplant value of the immunoglobulin free light chain²⁶.

High-dose chemotherapy and stem cell transplantation carry substantial risk, and there is an associated treatment-related mortality of approximately 15%²⁷. In 4 single-center studies, the day-100 mortality following stem cell transplant was 21%, but with poor patient selection has ranged as high as 39%^{28,29}. Deaths have been reported during stem cell mobilization and reflect the fragility of these patients and the risks of unanticipated fluid retention and pulmonary edema³⁰. Refinement of patient selection is critical to ensure improved outcomes for these patients. In 2 single-center trials, patients with ≤ 2 organ systems involved with amyloidosis had superior day-100 survival (81%) compared to those who had > 2 organs involved. Both the number of organs involved and the extent of cardiac involvement are major predictors of outcome³¹. Reducing the dose of melphalan helps reduce treatment-related toxicity but compromises response rate³². In a report from the Center for International Blood and Marrow Transplant Registry, 107 patients from 48 centers were reported. The 30-day treatment-related mortality was 18%; the median progression-free survival was 4 years. The most important predictor of survival was the experience of physicians at the transplant center³³. A prospective randomized study of 100 patients has been reported comparing high-dose therapy with melphalan and dexamethasone. This group of patients had an unusually high rate of treatment-related mortality, presumably an elevated risk on the basis of cardiac involvement³⁴. High-risk patients clearly do not benefit from high-dose therapy. The question of the efficacy of stem cell transplant and which patients are most appropriately served by this technique remains unsettled³⁵. Currently at Mayo Clinic, no more than one-quarter of patients with amyloidosis are eligible for stem cell transplantation. The high prevalence of cardiac involvement, delays in diagnosis, and renal insufficiency are all contraindications to considerations of high-dose therapy³⁶. Patient selection has a dramatic impact on outcome. When melphalan and dexamethasone was administered to a group of patients ineligible for stem cell transplantation in New York, the median survival was only 10.5 months, reflecting the difficulty in comparing results across phase II trials³⁷.

A phase II study using dexamethasone induction followed by high-dose melphalan in 30 patients with AL was reported. Of the 30 registered on study, 23 have been transplanted. Hematological response was seen in 52% of evaluable patients. The complete response rate after high-dose melphalan was 52%, a partial response in 43%, and organ response rate of 57%. There was no transplant-related mortality. Median overall survival has not been reached.

Overall survival was significantly better in those patients who achieved CR³⁸. Even in patients with moderate cardiac involvement due to AL, hematologic responses can be achieved in over two-thirds and cardiac responses in one-third of patients. Improved survival is associated with hematologic and organ responses. Cardiac biomarker improvement can be used as a measure of organ improvement and correlates with outcome³⁹.

4. Management of Amyloidosis with Novel Agent-Containing Regimens

Thalidomide—Sixteen patients were enrolled in a study of thalidomide; the maximum tolerated dose was 300 mg. Fifty percent experienced grade 3-4 toxicity. Twenty-five percent had to discontinue the medication. Twenty-five percent had a reduction in light chain proteinuria but not in total urinary protein⁴⁰. A second study of 12 patients reported drug-related toxicity in 75%, progressive renal insufficiency in 5, deep vein thrombosis and syncope in 2. The median time on thalidomide was 72 days⁴¹. A third report of thalidomide and dexamethasone therapy in 31 patients indicated that only 11 tolerated 400 mg a day, and the median time on study was 5.7 months with 20 experiencing grade 3 or greater toxicity⁴². Thalidomide and dexamethasone is active, but the toxicity is substantial. At Mayo Clinic, the median dose of thalidomide is only 50 mg a day; and at this dose, its efficacy may be limited. Symptomatic bradycardia has been reported in as many as 26%. Thalidomide has been combined with melphalan and dexamethasone in 22 patients with advanced cardiac amyloidosis. Eight hematologic responses and 4 organ responses were reported. Six patients died of advanced disease prior to cycle 3, a common finding in patients with cardiac amyloidosis⁴³.

Lenalidomide—Lenalidomide has been combined with dexamethasone in the treatment of AL. In a phase II trial, as a single agent in combination with dexamethasone, 34 patients received lenalidomide 25 mg per day. This dose was poorly tolerated and had to be reduced to 15 mg a day where tolerance was improved. Of 24 evaluable patients, 7 or 29% achieved a hematologic response and 8 or 38% achieved a partial hematologic response for an overall hematologic response rate of 67%. Fatigue and myelosuppression were each seen in 35%, thromboembolic complications were seen in 9%⁴⁴. Myelosuppression from lenalidomide occurred in a frequency seen in phase 2 trials in multiple myeloma. In a second trial, lenalidomide was administered and after 3 cycles, dexamethasone was added if a response had not been achieved. Twenty-three patients were enrolled, 13 previously treated, 10 patients discontinued treatment within the first 3 cycles of therapy due to rapid progression, death, or intolerance of treatment⁴⁵. There were 10 responses, 9 of whom required dexamethasone and 1 was achieved with lenalidomide alone. The responses were hematologic in 9, renal in 4, cardiac in 2, and hepatic in 2. The most common side effects were cytopenias, rash, and fatigue. With extended follow-up, the overall hematologic response rate was 41%, at a median follow-up of 33.6 months, 22 died. The median response duration and overall survival were 19.2 and 31 months, respectively. High-risk patients based on cardiac biomarkers were more likely to drop out early and were less likely to respond. High-risk patients had shorter progression-free and overall survival⁴⁶.

Lenalidomide has been combined with melphalan and dexamethasone in patients with newly diagnosed AL. In a phase I-II dose escalation study, the maximum tolerated dose of lenalidomide was 15 mg in combination with melphalan and dexamethasone. Hematologic and organ responses were observed in 68 and 50% of patients, respectively. A prospective phase III trial comparing melphalan and dexamethasone with melphalan, dexamethasone, and lenalidomide is planned. With a median follow-up of 12 months, 77% are alive; 6 deaths were observed, 5 due to progressive disease and 1 due to a secondary malignancy. The planned duration of therapy was nine 4-week cycles⁴⁷. Lenalidomide has also been combined with melphalan and dexamethasone using lenalidomide at a dose of only 10 mg per day. Six patients

were evaluable for response; 4 were previously untreated, and 2 had relapsed after stem cell transplant. Four out of 6 evaluable patients had a partial hematologic response, 2 were stable, and 1 died of progressive disease before the first cycle was completed. Four out of 6 patients required lenalidomide dose reductions ⁴⁸.

Lenalidomide has also been combined with low-dose dexamethasone and cyclophosphamide. In a phase I-II study, patients received 20 mg of dexamethasone for 4 consecutive days, cyclophosphamide at 100 mg per day for 10 consecutive days, and lenalidomide 15 mg 21 days out of 28. Seventy percent were previously untreated. The hematologic response rate for patients who received at least 2 cycles of treatment was 64% and for patients at the highest dose level, 75%. The median time to hematologic response was 2.5 months. Organ responses have been recorded in 5 patients. Lenalidomide, low-dose dexamethasone, and cyclophosphamide was an effective oral regimen for amyloidosis. An attenuated regimen also was available for patients with a serum creatinine >2.5 mg/dL with a high response rate ⁴⁹. A similar regimen of cyclophosphamide, lenalidomide, and dexamethasone was reported using lenalidomide at 15 mg per day. Twenty patients were enrolled, all were previously treated, and all were previously exposed to melphalan; 25% had previously received thalidomide. Grade 3 or 4 adverse events were seen in 60%. Four patients died after a median of 8 months due to heart failure and sudden death with a median follow-up of 9 months. Eight patients or 40% achieved a hematologic response complete in 1 (5%). Median time to response was 1.9 months. Organ response was reached in 3 patients. This regimen was effective in a cohort of heavily pretreated patients ⁵⁰.

At Mayo Clinic, we also have investigated lenalidomide, cyclophosphamide, and dexamethasone. Thirty-five patients were enrolled; 31% previously treated. The median number of cycles administered was 6. The most common nonhematologic toxicities were fatigue, edema, and rash. The overall hematologic response rate was 60%. Among patients receiving at least 4 cycles, the response rate was 87%. At least one organ response was documented in 24%. The median overall survival is 16.1 months. The median time to hematologic or organ progression was 6.7 months. Patients with a 50% reduction in free light chain had a superior overall survival. All 6 who died had significant cardiac involvement. Cyclophosphamide, lenalidomide, and dexamethasone had significant activity in patients with light chain amyloidosis. Toxicity is manageable, but patients with advanced cardiac involvement have a higher toxicity rate and risk of early discontinuation of therapy ⁵¹.

Bortezomib—By inhibiting proteasome function in plasma cells, bortezomib activates stress-activated protein kinase and mitochondrial apoptotic signaling ⁵². Amyloid-forming light chains can produce a load for the endoplasmic reticulum that makes these cells more sensitive to proteasome inhibition ⁵³. The National Amyloidosis Center in Britain reported 18 patients treated with bortezomib, half of whom received dexamethasone, all of whom had received prior thalidomide. A hematologic response was seen in 77% of patients, with 16% complete and 27% organ responses. The experience was updated to 20 patients with a response rate to bortezomib of 80%, with 15% complete responses. Forty percent had to discontinue therapy due to treatment-related toxicity ⁵⁴. A phase I dose-escalation study of bortezomib without steroids was recently reported. Two schedules were used, a biweekly schedule (days 1, 4, 8, and 11) in 21-day cycles and a weekly schedule (days 1, 8, 15, 22) in 35-day cycles. All patients were previously treated and were enrolled in 7 dose-escalating cohorts. Patients with grade III-IV cardiac disease were excluded from this study. The maximum dose was 1.6 mg/m² once weekly and 1.3 mg/m² twice weekly. Cessation and dose reductions for toxicity were reported in 12 and 4 patients, respectively. There were no treatment-related deaths. Hematologic responses occurred in 50% of 30 evaluable patients with 6 or 20% complete responses. Median time to first response was 1.2 months. In multiple myeloma, once-weekly bortezomib appears to be associated with less neurotoxicity ⁵⁵.

Eighteen patients, including 7 that had relapsed or progressed after prior therapy, were treated with bortezomib and dexamethasone. Bortezomib was given in a biweekly schedule, 2 weeks of 3 with dexamethasone 40 mg four days every 21. The hematologic response rate was 94%, complete in 44%, including patients who had failed prior high-dose dexamethasone. Twenty-five percent of patients had an organ response at a median of 4 months. Toxicity included neuropathy, fatigue, edema, and postural hypotension. Dose modification or cessation of therapy was required in 11. The optimal duration, durability, and tolerability of bortezomib remains undefined⁵⁶. Bortezomib has been combined with dexamethasone; 25 patients received 1.3 mg/m² days 1, 4, 8, 11 of a 21-day cycle. These patients were previously untreated. A hematologic response was observed in 56%, including 25% complete responses. Parameters of organ function improved in all complete responders. Grade 2 neurotoxicity was observed in 24%. These results confirmed the activity of bortezomib and dexamethasone in patients with AL⁵⁷.

Bortezomib and dexamethasone has also been used following risk-adapted melphalan and stem cell transplantation in an attempt to improve the depth of response. Thirty patients were enrolled. The day-100 stem cell transplant mortality was 12%. With a median follow-up of 20 months, the one-year posttransplant overall survival was 83%. The overall response rate posttransplant was 52%, with 22% complete responses. Seventeen of 23 patients received adjuvant bortezomib and dexamethasone. The hematologic response rate in those evaluable patients was 95% (18 of 19) with 74% (14 of 19) achieving a complete response. Organ responses were seen in 58%. Adjuvant bortezomib and dexamethasone following risk-adapted stem cell transplant was well tolerated and effective for eradicating persistent clonal plasma cell disease following stem cell transplant⁵⁸. A recent retrospective study reported a hematologic response in 71% within a median of 52 days, including 25% complete responses (CRs). Previously untreated patients had a 47% CR rate. A cardiac response was documented in 29% of patients, in most as sustained improvement of functional class^{58a}

Pomalidomide—Pomalidomide, a derivative of thalidomide with structural similarity to both lenalidomide and thalidomide was administered to 20 patients with 17 evaluable for toxicity. All were previously treated; 100% received prior alkylator, 44% prior lenalidomide, and 37% prior bortezomib. Neutropenia was the most common hematologic adverse event. The most common severe nonhematologic adverse event was fatigue. Median time on study was 3.7 months⁵⁹. Three patients discontinued therapy, 2 due to progression, 1 death 5 days into treatment. The potential of pomalidomide to produce responses with lower toxicity than other immunomodulatory drugs remains to be defined and will require further follow-up.

Conclusion

The optimal therapy for AL amyloidosis is unknown. Virtually all patients receive some form of cytotoxic chemotherapy. Stem cell transplant is widely used, but it is applicable to no more than one-quarter of patients. Combinations of dexamethasone, alkylating agents, immunomodulatory drugs, and bortezomib are all important considerations for the management of patients. A schema for the possible management of patients with amyloidosis is included in Figure 1.

POEMS Syndrome

5. Introduction

POEMS syndrome, also known as Crow-Fukase Syndrome, and Takatsuki syndrome, is a paraneoplastic disorder associated with an underlying plasma cell dyscrasia. The acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, *M* protein, and skin changes) captures several dominant features of the syndrome, but excludes other important traits like

elevated levels of vascular endothelial growth factor, sclerotic bone lesions, Castleman Disease, papilledema, peripheral edema, ascites, effusions, thrombocytosis, polycythemia, fatigue, clubbing and abnormal pulmonary function test. The major clinical feature of the syndrome is a chronic progressive polyneuropathy with a predominant motor disability.⁶⁰ Although the majority of patients have osteosclerotic myeloma, these same patients usually have only 5% bone marrow plasma cells or less (almost always monoclonal λ), and rarely have anemia, hypercalcemia or renal insufficiency. These characteristics and the superior median survival differentiate POEMS syndrome from multiple myeloma.

6. Pathogenesis

The pathogenesis of this multisystem disease is complex. Elevations of vascular endothelial growth factor and pro-inflammatory cytokines are the hallmark of this disorder⁶⁰. Little is known about the plasma cells except that more than 95% of the time they are λ light chain restricted with restricted V λ | germline gene usage⁶¹⁻⁶³. POEMS is not an immunoglobulin deposition disease. Aneuploidy and deletion of chromosome 13 have been described, but hyperdiploidy is not seen⁶⁴.

7. Clinical Features

Table 1 includes criteria for a diagnosis of POEMS syndrome^{60,65}. The peak incidence of the POEMS syndrome is in the 5th and 6th decades. Symptoms of peripheral neuropathy usually dominate the clinical picture. Symptoms begin in the feet and consist of tingling, paresthesias, and coldness. Motor involvement follows the sensory symptoms, and the former usually overshadows the latter. Both are distal, symmetric, and progressive with a gradual proximal spread. Severe weakness occurs in more than one-half of patients and results in inability to climb stairs, arise from a chair, or grip objects firmly with their hands. Impotence occurs, but autonomic symptoms are not a feature. The cranial nerves are not involved except for papilledema. Bone pain and fractures rarely occur. Patients report fatigue, which may be cytokine mediated or due to associated respiratory disease⁶⁶.

Hyperpigmentation is common. Coarse black hair may appear on the extremities. Other skin changes include skin thickening, rapid accumulation of glomeruloid angiomas, flushing, dependent rubor or acrocyanosis, white nails and clubbing. Testicular atrophy and gynecomastia may be present in men and galactorrhea in women. Pitting edema of the lower extremities is common. Ascites and pleural effusion occur in approximately one-third of patients^{60,67}. The liver is palpable in almost one-half of patients but splenomegaly and lymphadenopathy is found in fewer patients. On lymph node biopsy, in 11-30% the histology is angiofollicular lymph node hyperplasia (Castleman's Disease) or Castleman Disease-like.⁶⁰

Patients appear to be at increased risk for arterial and/or venous thromboses during their course, with nearly 20% of patients experiencing one of these complications^{60,68}. As many as one in ten patients present with a cerebral infarction⁶⁹.

8. Laboratory Investigations

Thrombocytosis is common, and polycythemia may be seen. Anemia and thrombocytopenia are not characteristic unless there is co-existing Castleman's Disease. Hypercalcemia and renal insufficiency are rarely present. The size of the M-protein on electrophoresis is small (median 1.1 g/dL) and is rarely more than 3.0 g/dL⁶⁷. The M-protein is usually IgG or IgA and almost always of the λ type. Renal dysfunction is usually not a dominant feature of this syndrome, but it is more common in those patients who have co-existing Castleman Disease. In our experience only 9% of patients have proteinuria exceeding 0.5 g/24 hours and 6% have a serum creatinine greater than or equal to 1.5 mg/dL. The renal histology is diverse with membranoproliferative

features and evidence of endothelial injury being most common ^{60,70}. Protein levels in the cerebrospinal fluid are elevated in virtually all patients. Bone marrow usually contains < 5% plasma cells, and when clonal cells are found they are almost always monoclonal λ .

Osteosclerotic lesions occur in approximately 95% of patients, and can be confused with benign bone islands, aneurysmal bone cysts, non-ossifying fibromas, and fibrous dysplasia. Some lesions are densely sclerotic, while others are lytic with a sclerotic rim, while still others have a mixed soap-bubble appearance. Bone windows of CT body images are often very informative, often even more so than FDG-uptake, which can be variable.

Endocrinopathy is a central but poorly understood feature of POEMS. In a recent large series from the Mayo Clinic ⁷¹, approximately 84% of patients had a recognized endocrinopathy, with hypogonadism as the most common endocrine abnormality, followed by thyroid abnormalities, glucose metabolism abnormalities, and lastly by adrenal insufficiency. The majority of patients have evidence of multiple endocrinopathies in the four major endocrine axes (gonadal, thyroid, glucose and adrenal).

Nerve conduction studies and electromyography demonstrate a polyneuropathy with prominent demyelination as well as features of axonal degeneration, which can be similar to the findings of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). CIDP is characterized by involvement of proximal as well as distal muscles, whereas POEMS neuropathy shows typical distal-dominant polyneuropathy. ^{71a}On nerve conduction studies, compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) are attenuated and frequently not elicited, these abnormalities are seen more commonly in lower limbs than upper limbs. Distal motor latencies are abnormally prolonged in motor nerves, and terminal latency indices are high ^{72,73}.

The pulmonary manifestations are protean, including pulmonary hypertension, restrictive lung disease, impaired neuromuscular respiratory function, and impaired diffusion capacity of carbon monoxide, but improve with effective therapy ^{66,74}. In a series of 20 patients with POEMS, followed over a 10-year period, 25% manifested pulmonary hypertension ⁷⁴. Whether the digital clubbing seen in POEMS is a reflection of underlying pulmonary hypertension and/or parenchymal disease is yet to be determined.

9. Differential Diagnosis

The dominant feature of this syndrome is typically the peripheral neuropathy, and not infrequently patients are initially diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) or, less frequently, Guillain-Barré. An algorithm for making the diagnosis is shown in Figure 2. If a monoclonal protein is detected, monoclonal gammopathy associated peripheral neuropathy and AL amyloidosis are considered. The two best ways to distinguish POEMS from these entities is to measure a plasma or serum VEGF level ⁷⁵ and to determine whether there are other POEMS syndrome symptoms or signs.

10. Prognosis

The course of POEMS syndrome is usually chronic with reported median survivals ranges from 33 months to nearly 14 years. The number of POEMS features does not affect survival ^{60,76}. In our experience, only fingernail clubbing and extravascular volume overload, i.e. effusions, edema, and ascites, were significantly associated with a shorter overall survival. More recently, we have identified respiratory symptoms to be predictive of adverse outcome ⁶⁶.

11. Therapy

There are no randomized controlled trials in patients with POEMS. Information about benefits of therapy is most typically derived retrospectively. Given these limitations, however, there are therapies which benefit patients with POEMS syndrome, including radiation therapy, alkylator based therapies, and corticosteroids⁶⁰. Intensive supportive care measures must also be instituted. Single or multiple osteosclerotic lesions in a limited area should be treated with radiation. More than 50% respond to irradiation.⁶⁷ If a patient has widespread osteosclerotic lesions or diffuse bone marrow plasmacytosis, systemic therapy is warranted. High-dose chemotherapy with peripheral blood transplant is yielding very promising results^{60,66}. When the selected therapy is effective, response of systemic symptoms and skin changes typically precede those of the neuropathy, with the former beginning to respond within a month, and the latter within 3 to 6 months with maximum benefit frequently not seen before 2 to 3 years. Clinical response to therapy correlates better with VEGF level than M-protein level^{77,78}, and complete hematological response is not required to derive substantial clinical benefit^{60,79}.

Based on retrospective data, approximately 40% of patients with POEMS syndrome will respond to low dose alkylator based therapy like melphalan and corticosteroids or cyclophosphamide and corticosteroids. Single agent corticosteroid will have temporary benefit in about 25% of patients. If the patient is considered to be a candidate for peripheral blood stem cell transplantation, melphalan-containing regimens should be avoided until after stem cell harvest.

High-dose chemotherapy with peripheral blood stem cell transplant is an emerging therapy for patients with POEMS^{60,79}. All patients had improvement of their neuropathy over time; as in the case with radiation therapy and other chemotherapy, improvement of the peripheral neuropathy takes months to years. Other clinical features improve after stem cell transplantation, including levels of VEGF⁸⁰. Among the first 16 patients we transplanted, the treatment related morbidity was higher than expected with more than one-third requiring mechanical ventilation. We subsequently looked at our experience with 30 patients undergoing stem cell transplant and found that from day 8 to 16 patients with POEMS had higher than expected rates of fever, diarrhea, weight gain, and rash (93%, 77%, 53%, and 43%, respectively), and up to 50% had an engraftment-like syndrome that appeared to be corticosteroid responsive⁷⁹. Splenomegaly was the baseline factor that best predicted for a complicated peri-transplant course. Patients had a higher than expected transfusion need with median numbers of platelet and erythrocyte transfusions being 5 apheresis units and 6 units, respectively. They also had delayed engraftment with a median time to neutrophil engraftment of 16 days, with only 10 % engrafting by day 13. Their times to platelets $20 \times 10^9/L$ and $50 \times 10^9/L$ were 14.5 days and 19.5 days, respectively.

There have been case reports of using plasmapheresis, intravenous immunoglobulin, interferon-alpha, tamoxifen, trans-retinoic acid, thalidomide, ticlopidine, argatroban, strontium-89, bevacizumab, and lenalidomide⁶⁰. Neither plasmapheresis nor intravenous immunoglobulin is effective. Although there is a theoretical rationale (anti-vascular endothelial growth factor and anti-tumor necrosis factor effects) for using thalidomide in POEMS patients⁸¹⁻⁸⁴, enthusiasm for its use should be tempered by the high rate of peripheral neuropathy induced by the drug. No systematic study has addressed the incidence of thalidomide neuropathy in POEMS so this recommendation is based on the experience with neurotoxicity seen in myeloma and amyloidosis. In contrast, the next generation immune modulatory drug, lenalidomide, has a much lower risk of peripheral neuropathy. We have observed dramatic improvements in one patient treated with this drug⁸⁵. In France, nine patients, one of whom was newly diagnosed, were treated with lenalidomide and dexamethasone⁸⁶. Serious side effects were noted in 3 patients with 2 hematologic toxicities and a cutaneous allergy. All evaluable had at least a partial hematologic response, and clinical responses, including

improvement in performance status and neurologic symptoms, were documented among the 8 who had sufficient follow-up. One patient relapsed 5 months after discontinuing therapy, but responded to reintroduction of the drug. Bortezomib use has been reported in 2 patients^{87,88}. The first report is difficult to interpret since the patient had a number of chemotherapies prior to receiving a bortezomib, doxorubicin, and dexamethasone combination. There was early evidence of improvement even before starting the bortezomib regimen. The second report is more convincing, 7 cycles of bortezomib and dexamethasone resulted in patient improvement. Although an anti-VEGF strategy is appealing, the results with bevacizumab have been mixed^{84,89-93}. Two patients who had also received alkylator during and/or predating bevacizumab had benefit. Three patients receiving it died. Another had improvement, but was then consolidated with HSCT.

The physical limitations of the patient should not be overlooked while evaluating and/or treating the underlying plasma cell disorder. As always, a multidisciplinary, thoughtful treatment program will improve a complex patient's treatment outcome. A physical therapy and occupational therapy program is essential to maintain flexibility and assist in lifestyle management despite the neuropathy. In those patients with respiratory muscle weakness and/or pulmonary hypertension, overnight oxygen or continuous positive airway pressure (CPAP) may be useful.

12. Conclusions

POEMS Syndrome is a complex syndrome that shares elements with other diseases—most notably other plasma cell dyscrasias and Castleman's Disease. Significant clues to the underlying pathogenesis lies in the monoclonal lambda light chain restriction, the osteosclerotic lesions, and VEGF levels. The best treatments are those that are useful to treat patients with myeloma, although neurotoxic therapies should be applied sparingly (if at all), limiting the treatment armamentarium. One of the greatest practical challenges is making the diagnosis in a timely fashion to prevent severe irreversible neurological disability.

13. Expert Opinion

Amyloidosis and POEMS syndrome are rare plasma cell dyscrasias. The clinical manifestations of these clonal, nonproliferative disorders are not related to the total tumor burden, as it is in multiple myeloma, but due to synthetic products from the plasma cell that result in the manifestations characteristic of these disorders. For a quarter of a century, ending in 1985, standard alkylator and steroid therapy were administered for these disorders. Complete suppression of the synthetic product of the plasma cells was not frequently achieved, and outcomes were predictably poor with median survivals in amyloidosis ranging in the 12-month range and stabilization or regression of the cardiopulmonary and neuropathic manifestations of POEMS syndrome uncommon. In 1996 stem cell transplantation was introduced for these disorders and with high-dose therapy, both disorders showed a significant improvement in outcome with longer survival and improved quality of life for these patients.

Since both disorders are uncommon, phase III trials of chemotherapy are rare. Comparisons of multiple phase II trials suffer from the heterogeneity of the patient populations, making it difficult to objectively determine which therapies among the multiple choices are superior. Nonetheless, high-dose therapy has clearly been a major step forward for these disorders. Beginning in 1990, the introduction of targeted therapies, both the IMiD's and proteasome inhibition, has resulted in further improvements in outcomes. The current literature is focusing on the use of novel agents as an alternative to high-dose therapy. Studies are also underway that are looking at novel agent induction prior to high-dose therapy as well as posttransplantation consolidation with novel agents in an attempt to increase the depth of response in these rare disorders. The ultimate goal of therapy in these disorders is not

necessarily a complete suppression of the number of clonal plasma cells. In amyloidosis, sufficient suppression of light chain production that results in solubilization of the misfolded amyloid fibril protein will suffice. In POEMS, suppression of the chemical mediators responsible for the neurotoxicity and cardiopulmonary manifestations is sought.

Challenges to advances in the field includes a low level of recognition of these disorders, which frequently are diagnosed too late for any therapy to be effective. This is due to the fact that there is no single blood test or imaging study that is diagnostic for these diseases. The differential diagnosis must be kept in mind and then the diagnosis must be aggressively sought.

In amyloidosis, reports on the use of bortezomib have generated a great deal of enthusiasm because of the high hematologic and organ response rates that are reported using this drug as a single agent. In POEMS syndrome, reducing the toxicity of high-dose therapy, the high risk of engraftment syndrome, and cardiorespiratory decompensation during the neutropenic phase of chemotherapy are major foci for research. Better understanding of the role that vascular endothelial growth factor (VEGF) plays in the pathophysiology of the syndrome is actively being pursued.

Recognition of the complex of a combination of peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder (typically λ), skin changes, papilledema, extravascular volume overload (peripheral edema, pleural effusions, ascites), sclerotic bone lesions, thrombocytosis, Castleman disease, increased levels of circulating vascular endothelial growth factor, and abnormal pulmonary function tests is the first step in diagnosing POEMS syndrome. For those patients with a dominant sclerotic plasmacytoma, first line therapy is radiation. Patients with diffuse sclerotic lesions or absence of any bone lesion and for those who have not demonstrated stabilization of their disease 3 to 6 months after completing radiation therapy should receive systemic therapy. Useful approaches include therapy with corticosteroids, low dose alkylator therapy, and high-dose chemotherapy with peripheral blood stem cell transplant. The role of anti-VEGF therapies, immune modulatory drugs, and proteasome inhibitors has not yet been defined, but drugs with known high rates of treatment related neuropathy should not be considered as first line therapy.

Article highlights box

Amyloidosis

- All patients with AL amyloidosis are candidates for a trial of chemotherapy.
- Melphalan dexamethasone, is a standard for transplant ineligible patients
- Lenalidomide, and bortezomib show activity in treating amyloidosis

POEMS

- A high suspicion for the diagnosis of POEMS is required in patients with monoclonal gammopathy and neuropathy, especially if they have any other unusual symptoms, including thrombocytosis
- Once the diagnosis is made, a thorough evaluation of a patient's baseline characteristics is required including objective neurological exam, endocrine evaluation, bone radiographs (CT bone preferred), pulmonary evaluation, and VEGF levels.
- Treatments can be highly effective, but one must be cautious not to jump from one therapy to another too quickly since clinical responses are typically not apparent for at least 3-6 months and continue to improve for years.

- Radiation therapy should be considered for patients with a bone marrow biopsy negative for clonal plasma cells if 3 or fewer bone lesions are seen on computed tomography of the body.
- High-dose melphalan with autologous stem cell transplant should be considered as first line therapy for younger patients. Other less intensive alkylator based therapy or the combination of lenalidomide and dexamethasone can also be considered, but thromboprophylaxis is imperative for those receiving the latter combination.
- Thalidomide, bevacizumab, and bortezomib cannot be recommended as first line therapy based on current available data

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Treatment of AL Amyloidosis– off-study

*http://msmart.org/msmart_mar09_002.htm

Figure 1.
Algorithym for management of amyloidosis

DEMYELINATING PERIPHERAL NEUROPATHY				
Monoclonal gammopathy (λ)		OSTEOSCLEROTIC LESIONS OR CASTLEMAN DISEASE	Increased VEGF	
YES	+	YES	+	DIAGNOSIS Definite
NO, but biopsy proven plasmacytoma	+	YES	+	Definite
YES	+	NO	+	Probable*
YES	+	YES	+	Probable*
NO, but biopsy proven plasmacytoma	+	YES	+	Possible*
NO	+	NO	+	Possible*

Figure 2.
An algorithm for making the diagnosis.

Table 1Criteria for the Diagnosis of POEMS Syndrome^{60,65}

Major criteria	1. Polyneuropathy* (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder* (almost always λ)
	3. Castleman disease*
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid, [†] pituitary, gonadal, parathyroid, pancreatic [‡])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis / polycythemia [‡]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B ₁₂ values

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

* Polyneuropathy and monoclonal plasma cell disorder or Castleman Disease are present in all patients; to make diagnosis at least one other major criterion and 1 minor criterion is required to make diagnosis. A definite diagnosis is defined by 3 major criteria and at least 1 minor criterion, and a probable diagnosis is defined by 2 major criteria, with at least 1 minor criterion

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

[‡] Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present

Table 2

Novel Agents in the therapy of POEMS

Regimen	
Thal after MP ⁸¹	No hematological response but improved ascites; stabilized PN, splenomegaly, pulmonary hypertension
Thal + Dex after CAD ⁸²	CD/POEMS: improved ascites, effusions, pulmonary hypertension, PN, renal function, IL-6 level
Thal + Dex ⁸³	N = 9; VEGF improved in all; PN improved in 66%; stable in 33%; improved edema; no HCR
Thal after VAD, CTX, bevacizumab ⁸⁴	Improved cardiopulmonary status, but no improved PN and rising VEGF
Lenalidomide + Dex ⁸⁵	Improved ascites, PS, PN, VEGF, testosterone, pulmonary function tests
Lenalidomide+ Dex ⁸⁶	N=9; all had hematologic response; clinical responses in all evaluable patients including PS, neurological syndrome, edema, and VEGF.
Bortez+AD after VAD, CMP, and AD ⁸⁷	Improved M-protein, VEGF, paresthesias, splenomegaly, effusions, muscle strength, gynecomastia, and skin changes
Bortez + Dex ⁸⁸	Improved M-protein, polyneuropathy, hepatomegaly, testosterone; no change in electromyelography
Bevacizumab alone ⁹⁴	Death within 6 weeks
Bevacizumab alone ⁹⁰	Worsening PN, anasarca, multiorgan failure; died of pneumonia 5 weeks after therapy
Bevacizumab alone ⁹¹	Improved pain, breathing, walking
Bevacizumab + Mel-Dex ⁸⁹	Improved effusions/ascites
Prior VAD/CTX ⁸⁴	Improved edema, pain, weakness, VEGF
Bevacizumab + CTX-Dex ⁹³	Initial worsening; repeat with bevacizumab → improved pulmonary HTN, anasarca, skin changes
Bevacizumab + CTX-CS ⁹²	Initial improvement, but multiorgan failure and death

HCR = hematological complete response; PN = polyneuropathy; PS = performance status.

Bortez, bortezomib; CS = corticosteroids; CTX, cyclophosphamide; Dex, dexamethasone; HTN, hypertension; Len, lenalidomide; Mel, melphalan; PS, performance status; VAD, vincristine, doxorubicin, dexamethasone; VEGF, vascular endothelial growth factor.