Dose-Intensive Melphalan With Blood Stem Cell Support for the Treatment of AL Amyloidosis: One-Year Follow-up in Five Patients

By Raymond L. Comenzo, Evan Vosburgh, Robert W. Simms, Peter Bergethon, Diane Sarnacki, Kathleen Finn, Simon Dubrey, Douglas V. Faller, Daniel G. Wright, Rodney H. Falk, and Martha Skinner

The morbidity and lethality of AL amyloidosis is caused by the deposition of Ig light chains as fibrillar amyloid protein in vital organs, disrupting their function, and not by the generally low burden of clonal plasma cells that produce the paraproteins. Survival of patients with AL amyloidosis is no more than 1 to 2 years from the time of diagnosis with current management approaches. Clearly, more effective therapies are needed for this rapidly lethal disease. Five patients were treated with dose-intensive melphalan and blood stem cell support and followed for a period of 1 year. Patients were diagnosed with AL amyloidosis by tissue biopsy and categorized by performance status and organ involvement. Their plasma cell dyscrasias were evaluated with immunofixation electrophoresis of serum and urine specimens, quantitative serum Ig, and immunohistochemical staining of bone marrow biopsy specimens. After treatment with dose-intensive intravenous melphalan followed by infusion of autologous growth-factor–mobilized blood stem cells, clinical evaluations and plasma cell studies were repeated at 3 and 12 months. Three men and 2 women aged 38 to 53 years were treated. Median performance status (SWOG) was 2 (1 to 3), and clinical presentations included nephrotic syndrome (n = 1), symptomatic cardiomyopathy (n = 1), gastrointestinal involvement with polyneuropathy (n = 2), and hepatomegaly (n = 1). With a median follow-up of 15 months (12 to 17 months), all five patients are well and have shown stable or improved performance status and clinical remission of organ-related dysfunction, including a 50% reduction in daily proteinuria with no change in creatinine, reversal of symptoms of cardiomyopathy and reductions of posterior wall and septal thickening, reversal of polyneuropathy and gastric atony, and resolution of hepatomegaly by computed tomographic scan. In 3 of the 5 patients (60%) at 12 months after treatment, plasma cell dyscrasias could not be detected. Dose-intensive chemotherapy with intravenous melphalan and growth-factor–mobilized blood stem cell support is feasible therapy for patients with AL amyloidosis, even when there is clinical evidence of cardiac involvement. At least some patients with AL amyloidosis achieve complete remission of their plasma cell dyscrasia, improvement in performance status, and clinical remission of organ-specific disease after this form of treatment.

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Table 1. SWOG Patient Performance Status Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Scale</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active; able to carry on all predisease activities without restriction. (Karnofsky 90% to 100%)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature, eg, light housework or office work. (Karnofsky 70% to 80%)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to perform any work activities. Up and about more than 50% of waking hours. (Karnofsky 50% to 60%)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 40% to 50%)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot perform any self-care. Totally confined to bed or chair. (Karnofsky 10% to 20%)</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
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RESULTS

Patients

Between January 1, 1994 and December 31, 1994, three men and two women with a median age of 46 years (range, 39 to 53) were treated on this trial. All patients gave written informed consent. We report the 1 year follow-up results in these five consecutive patients who had multiple biopsies from separate sites positive for amyloid (range, 2 to 4) and who were treated at a median of 5 months from diagnosis (range, 2 to 18 months). All of these patients had evidence of amyloid deposits in blood vessels in BM biopsies.

All patients tolerated stem cell mobilization and leukaphereses without significant complications. Per kilogram of patient weight, the five patients received a median of $8.3 \times 10^8$ CD34+ cells (3.4 to 12.5) containing $100 \times 10^4$ CFU-GM (33 to 133). All patients tolerated dose-intensive melphalan and stem cell infusion (days -4 to 0) without significant complications, and became pancytopenic after dose-intensive melphalan. Hematopoietic reconstitution occurred in all patients by a median of 10 days for neutrophils (range, 9 to 10) and for platelets (9 to 12). At 12 months in these five patients, median complete blood count values were white blood cell count $5.0 \times 10^9/L$ (4.6 to 5.6), hemoglobin 13.8 gm/dL (13.3 to 15.6) and platelet count $156 \times 10^9/L$ (118 to 208).

All patients had nausea, vomiting, and grade II mucositis by the Common Cancer Toxicity Criteria. One patient became febrile requiring IV antibiotics; blood cultures were negative. Two patients had peripheral and pulmonary edema requiring diuresis. Other toxicities included hypernatremia and hyponatremia and increased creatinine. All toxicities resolved within 30 days of therapy.

Patient Responses at 12 Months

Case one Patient 1, a 42-year-old man, had gastrointestinal symptoms and peripheral polyneuropathy, and was treated 2 months from diagnosis, having received no prior oral therapy. He had presented with a painful peripheral polyneuropathy, was orthostatic by vital signs with symptoms, and had gastrointestinal symptoms that included dysgeusia, loss of appetite, nausea, and vomiting. Biopsy specimens of stomach, rectum, BM (1+), and abdominal fat were positive for amyloid. Sural nerve biopsy was negative. He required total parenteral nutrition (TPN) for profound (25%) weight loss due to gastric atony as documented by a gastric emptying scan showing 0% emptying at 2 hours. Opiates were required for discomfort associated with his peripheral neuropathy.

At 12 months he had regained all lost weight, was eating a normal diet without TPN, and had a gastric emptying scan in the supranormal range. A dramatic improvement in performance status was noted, from 3 to 0, and he had returned to full-time employment. He required no medications. As shown in Fig 1, depicting the neurologic exams of this patient across the top, the polyneuropathy had remitted at 3
months, resulting in improved overall function. Resolution of orthostatic and gastrointestinal symptoms occurred 3 to 9 months after dose-intensive melphalan.

At baseline, this patient had serum and urine findings of a plasma cell dyscrasia with a monoclonal IgA λ in his serum and λ light chains in his urine, as well as suppressed noninvolved Ig levels, and a BM biopsy showing 10% plasma cells uniformly staining for λ. At 12 months, his BM showed less than 5% plasma cells with staining for both light-chain isotypes, and he had negative IFE-S and IFE-U. IgA and IgM were normal but IgG was 630 mg/dL (normal, 700 to 1,600 mg/dL).

**Case two.** Patient 2, a 46-year-old man with amyloid cardiomyopathy and a myocardial biopsy sample positive for amyloid, was treated 5 months after diagnosis having received a single course of oral melphalan and prednisone containing 32 mg of melphalan. BM (1+) and abdominal fat biopsies were also positive for amyloid. At 12 months of follow-up, performance status over the year improved from 2 to 0, New York Heart Association (NYHA) class improved from III to I, diuretics were no longer needed, and the patient was able to work full-time and exercise strenuously.

A comparison of echocardiograms from baseline and 12 months posttherapy showed reductions in the thickness of both the posterior wall and interventricular septum from 1.5 and 1.4 cm to 0.93 and 0.98 cm, respectively, although left ventricular ejection fraction decreased from 56% at baseline to 44% at 12 months. Baseline IFE-S was negative while baseline IFE-U showed λ light chains. Baseline BM studies showed 10% plasma cells uniformly staining for λ. Although the BM findings at 12 months follow-up had normalized, showing less than 5% plasma cells staining for both light-chain isotypes; although the IFE-S remained negative and the serum IgG level had normalized, increasing from 544 to 960 mg/dL; and, although quantitative urinary λ light chains were not detectable, IFE-U showed a faint band suggestive of λ light chains, a band that had not been detected at 3 months of follow-up. In addition, 24-hour urinary protein increased from 256 mg at baseline to 601 mg at 12 months.
with unchanged albumin and creatinine, and alkaline phosphatase increased also, from 104 to 277 U/L. The significance of these findings is not clear at this time, in view of the patient’s excellent performance status. (Author’s note: At 2 years posttherapy, IFE-U, IFE-S, and BM were normal and complete remission maintained.)

Case three. Patient 3, a 38-year-old man treated 3 months after diagnosis, presented with a painful peripheral polyneuropathy, orthostasis, nausea, abdominal pain, and profound weight loss (55 lb) because of gastric atony. Biopsy specimens of an axillary lymph node, abdominal fat, and BM (2+) were positive for amyloid. He had a performance status of 3 and had received no prior therapy. Opiates were required to treat pain due to his peripheral neuropathy. He had λ light chains in both serum and urine and 5% plasma cells in his BM.

As was the case for patient 1, the peripheral polyneuropathy, gastrointestinal, and autonomic symptoms resolved over the 12 months after dose-intensive melphalan and no medications were needed or prescribed. The pattern of resolution of his neuropathic symptoms is depicted in the lower panels of Fig 1. Initially the patient required total parenteral nutrition for several months, but by 1 year’s time he was eating a normal diet, had regained 30 lb, and returned to full-time employment. Performance status had improved from 3 to 0. BM biopsy sample was normal and IFE-U and IFE-S were negative.

Case four. Patient 4, a 46-year-old woman with hepatomegaly and AL amyloidosis confirmed by liver biopsy specimen, was treated 11 months after diagnosis having received oral therapy including 264 mg of melphalan. At 12 months’ follow-up, performance status improved from 2 to 0 and cranio-caudal liver span by CT scan decreased from 20 cm at baseline to 14.5 cm, demonstrating resolution of hepatomegaly. This patient’s formal abdominal girth measurements over the same period showed a 3-cm decrease without weight change, and alkaline phosphatase decreased from 184 to 136 U/L.

Baseline BM findings showed 12% uniformly κ-staining plasma cells, and, although baseline IFE-S was negative, baseline IFE-U showed κ light chains. At 12 months' follow-up, BM studies were normal, IFE-S remained negative, and previously noted urinary light chains were not detected by IFE-U. Serum IgG and IgA levels had been suppressed at baseline, whereas, at 12 months, the IgG level had increased to 911 mg/dL, but the IgA level remained below normal. With respect to other organ systems, 24-hour urinary protein was reduced from 645 to 90 mg with creatinine unchanged at 1.3 mg/dL, and echocardiogram remained normal.

Case five. Patient 5, a 53-year-old woman with nephrotic syndrome, had had a monoclonal gammapathy of undetermined significance for 15 years before being diagnosed with multiple myeloma and AL amyloidosis. Renal and abdominal fat biopsy specimens were positive for amyloid. At diagnosis, serum IgGκ was 3.5 g/dL, IFE-U contained monoclonal IgGκ, and BM biopsy had 25% λ-staining plasma cells in sheets. After treatment with oral therapy, including 468 mg of melphalan, a reduction in monoclonal paraprotein to 1.3 g/dL was observed. She was treated with dose-intensive IV melphalan and stem cell support 18 months after myeloma and amyloidosis were diagnosed. At 1 year posttherapy, her performance status remains a 1 with no evidence of progressive amyloidosis.

Of note, the daily urinary protein has decreased from 11,370 mg at the time of stem cell mobilization to 5,040 mg 12 months later, with a creatinine of 1.0 versus a baseline of 1.1 mg/dL. The serum albumin has increased to 3.4 from a baseline of 2.0 g/dL. However, the monoclonal IgGκ remained detectable by IFE-S and IFE-U; serum Ig levels were otherwise normal.

DISCUSSION

AL amyloidosis is a rapidly lethal disease, and therapies currently in use have modified its dismal prognosis only marginally. In a recent trial, 100 patients with AL amyloidosis were prospectively randomized to receive colchicine alone or melphalan, prednisone, and colchicine.14 Median survival from the time of study entry to end-organ failure in those treated with three drugs was 12.2 months, compared with 6.7 months for those treated with colchicine alone (P = .087). In an earlier study of 101 patients, the progression-free median survival for those receiving melphalan and prednisone was 16 months whereas for controls receiving colchicine it was 6 months.6 Moreover, evaluation of patient subsets in this study showed differences in response to chemotherapy.

Of particular note, none of the 15 patients with polyneuropathy that were studied were found to respond to treatment with oral melphalan and prednisone. Each of these patients experienced progression of their disease without enhanced survival. In contrast, survival for patients with congestive heart failure was significantly longer for those receiving melphalan and prednisone, a median survival of 12 months, versus 5 months for controls. Among patients with nephrotic syndrome there was no survival difference based on regimen.

It is against the backdrop of these two prior clinical trials that the significance of this report can be best appreciated, for these trials indicate that oral melphalan, despite its variable solubility and its short-term hematologic and gastrointestinal toxicities,
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with minimal morbidity, despite prior evidence of amyloid cardiac disease. In this regard, clinical trials using dose-intensive chemotherapy with mobilized blood stem cells for patients with AL amyloidosis should be designed so that the toxicities of the stem cell mobilization regimen do not prevent patients from being treated with dose-intensive melphalan. Our results support the advisability of using growth factor mobilization of stem cells and of dispensing with cyclophosphamide-based mobilization regimens, and their potential infectious and myocardial side effects.

In view of prior clinical trials, it is notable that three of five patients experienced durable complete remissions of plasma cell dyscrasias and that all patients experienced improved organ function in the predominant organs of involvement. It is particularly notable that two patients with painful polynuropathy experienced remissions of neuropathic symptoms after treatment, for the polyneuropathy associated with amyloidosis has been recalcitrant to alternative treatment approaches.\(^2,21\) Indeed, a treatment-associated improvement in sensory and motor function has never been reported previously in patients with this disease. The rapid reversal of neuropathic signs and symptoms that we observed questions the commonly held belief that infiltration and compression of vascular and neural elements by amyloid deposits underlie its pathophysiology. Rather, remission of polynuropathy with a reduction of amyloidogenic plasma cells supports the conclusion that a readily reversible metabolic derangement associated with Ig aggregation into amyloid fibrils may be the pathophysiological mechanism that underlies the polyneuropathy in this disease.

Although allogeneic transplantation in select patients with AL amyloidosis may be feasible,\(^22,24\) the organ compromise of patients with AL amyloidosis may increase the risk of this approach. However, allogeneic BM would be free of contaminating clonal cells whereas mobilized autologous blood stem cell preparations may contain clonal plasma cell precursors.\(^25,27\) Ex vivo treatment of autologous stem cell preparations to remove contaminating neoplastic cells may prove important for maximizing efficacy of this treatment approach.\(^28\) Hence, ex vivo purging procedures, combined with polymerase chain reaction assays for molecular markers of clonal cells, may be useful in the development of future clinical trials.\(^29-31\)

In conclusion, AL amyloidosis, often a rapidly fatal plasma cell dyscrasia, is amenable to treatment with dose-intensive IV melphalan, followed by growth-factor–mobilized blood stem cell support for hematopoietic rescue. Remissions of both the plasma cell dyscrasia and clinical symptoms and signs of amyloidosis occur with this treatment approach; furthermore, objective amelioration of amyloid-related organ dysfunction may occur despite persistence of the plasma cell dyscrasia. The durability of the clinical remissions achieved by this treatment approach remains to be determined, as does the impact of this approach on resorption of amyloid deposits and patient survival. Nevertheless, our results indicate that this therapy can be conducted safely in patients with AL amyloidosis and that dramatic clinical improvements can be achieved.

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