Successful Treatment of Scleromyxedema With Autologous Peripheral Blood Stem Cell Transplantation

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Background: Scleromyxedema is a rare chronic fibromucinous disorder that can have devastating clinical manifestations, including sclerosis of the skin with progressive pharyngeal and upper airway involvement, resulting in high mortality due to respiratory complications. Herein we describe a novel therapeutic approach. Because autologous hematopoietic stem cell transplantation is effective in other plasma cell proliferative disorders, it may be effective in this setting.

Observations: We retrospectively evaluated 6 patients who were offered high-dose chemotherapy with stem cell rescue as treatment for scleromyxedema. One heavily pretreated patient was unable to mobilize stem cells. The remaining 5 patients mobilized stem cells and underwent successful transplantation. There was no treatment-related mortality. Hematologic responses were seen in 4 patients, including 2 complete remissions and 2 partial remissions, and all 4 had improvement in extracutaneous manifestations. All 4 patients subsequently had relapse of the monoclonal protein, and 3 developed skin relapses at 14, 37, and 45 months.

Conclusions: High-dose chemotherapy with stem cell rescue is feasible for patients with scleromyxedema and, although not curative, offers durable remission in most patients. This therapy should be considered before treatment with alkylating agents or other treatments that could adversely affect the ability to collect stem cells.

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Scleromyxedema, also known as “generalized lichen myxedematous,” is a rare chronic cutaneous fibromucinous disorder of unknown cause. Scleromyxedema was first described in 1953 by Montgomery and Underwood. The classification was revised in 2001 by Rongioletti and Rebora. To make the diagnosis, the patient must fulfill the following 4 criteria: (1) generalized papular and sclerodermoid eruption; (2) mucin deposition, fibroblast proliferation, and fibrosis; (3) monoclonal gammapathy; and (4) the absence of thyroid disease. Scleromyxedema presents with a papular lichenoid eruption, with sclerosing skin infiltration due to the deposition of glycosaminoglycan in the papular and reticular dermis. The skin eruption includes papular mucinosis or waxy papules, with a predilection for sun-exposed areas, including the face, neck, upper trunk, forearms, hands, and thighs. On the face, the infiltrating lesions may cause characteristically leonine facies. As the disease progresses, the skin infiltration becomes widespread, with sclerosis. These sclerodermalike features produce significant disability. Scleromyxedema is associated with a monoclonal protein, predominantly IgGA, but can be associated with other isotypes. Extracutaneous manifestations include neurologic complications, such as encephalopathy and seizures; gastrointestinal dysmotility and malabsorption; rheumatologic problems, including joint contractures and muscle weakness; pulmonary complications, such as restrictive or obstructive lung disease; reduced diffusing capacity; and upper airway dysfunction and cardiovascular complications, such as pulmonary hypertension. Scleromyxedema has a chronic progressive course, with a high mortality rate due to progressive debilitation and respiratory complications.

Treatment for scleromyxedema has proved unsatisfactory. Treatment options have included agents aimed at eradicating the plasma cell clone, such as chemotherapy, glucocorticoids, and thalidomide, as well as treatments aimed at blocking the paraneoplastic effects of the plasma cell clone, such as intravenous immunoglobulin, extracorporeal photopheresis, psoralen–UV-A, and electro...
tron beam, topical corticosteroids, interferon alfa, and retinoids. Feasel et al described a patient who achieved remission following high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT). Peripheral blood stem cell transplantation has been used successfully to treat multiple myeloma and other nonmalignant plasma cell proliferative diseases that are associated with a low tumor burden, such as primary systemic amyloidosis and POEMS syndrome (ie, a syndrome variously combining peripheral neuropathy, visceromegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Based on this, we elected to offer high-dose chemotherapy followed by stem cell rescue to patients with scleromyxedema.

A highly sensitive serum free light chain (FLC) assay has recently been introduced in clinical practice. It uses a nephelometric assay to quantify k and λ FLCs that are not bound to intact immunoglobulin. Monoclonal elevations can be reliably distinguished from polyclonal elevations using the k:λ ratio. The serum FLC k:λ ratio had a sensitivity of 98% to 99% in detecting monoclonal light chains in patients with primary amyloidosis and a specificity of 100% among 282 healthy control subjects. The assay is used to monitor light chain multiple myeloma, amyloidosis, and nonsecretory multiple myeloma. We explored whether the serum FLC was abnormal in scleromyxedema and examined if FLC response correlates with clinical response to PBSCT.

## METHODS

### PATIENTS

Six patients with scleromyxedema were referred for treatment with high-dose chemotherapy and autologous PBSCT between March 18, 1999, and December 13, 2004. All patients had provided written informed consent for use of their medical records. Approval of the Mayo Foundation Institutional Review Board was obtained, in accord with federal regulations and the Declaration of Helsinki.

Frozen serum samples from before and after PBSCT were available for study in all 5 patients who underwent PBSCT. Free light chain estimation was carried out using a serum FLC assay (Freelite®; The Binding Site Limited, Birmingham, England) performed on a nephelometer (Dade Behring Inc, Deerfield, Ill). The FLC estimation consisted of 2 separate assays, one to detect k FLCs and the other to detect λ FLCs. The levels of FLCs were used to assess clonality based on the ratio of k:λ light chain levels. The normal range for k FLCs is 0.33 to 1.94 mg/dL, whereas the normal range for λ FLCs is 0.57 to 2.63 mg/dL in this assay. For the k:λ ratio, 0.26:1.65 is the normal value. Patients with ratios less than 0.26 are classified as having a monoclonal k FLC, and those with ratios greater than 1.65 are classified as having a monoclonal λ FLC.

### TREATMENT

#### Stem Cell Mobilization

Four patients mobilized stem cells using cyclophosphamide followed by growth factor injections. Stem cells were collected after administration of cyclophosphamide, 1.5 g/m² per day, for 2 consecutive days. This was followed by sargramostim (granulocyte-macrophage colony-stimulating factor) or filgrastim (granulocyte colony-stimulating factor) at 5 µg/kg starting on day 3 and continuing until the collection was complete. Apheresis was performed once the total white blood cell count exceeded 500 cells/µL. The remaining 2 patients had stem cells collected using filgrastim (granulocyte colony-stimulating factor) alone, administered subcutaneously (3 µg/kg) daily until the completion of peripheral blood stem cell collection, with apheresis beginning on the fifth day after starting filgrastim. The target goal for the apheresis procedure was 5×10⁶ CD34 cells per kilogram.

#### Conditioning Regimen

Following stem cell harvest, all patients proceeded to transplantation. Four patients received a conditioning regimen consisting of melphalan, 100 mg/m², given daily on days −2 and −1. The fifth patient, in whom the dose was reduced because of severe pulmonary hypertension, received a conditioning regimen consisting of melphalan, 70 mg/m², given on days −2 and −1. Stem cells were infused on day 0.

#### Supportive Care

Supportive care was standard for transplantation patients, including prophylactic levofloxacin, penicillin, acyclovir sodium, and fluconazole. Patients were treated as outpatients but were hospitalized for persistent neutropenic fever, severe nau-
sea and vomiting, or intractable mucositis or dehydration. Sar-ogramostim, 5 µg/kg subcutaneously, was given daily until the absolute white blood cell count was greater than 1000 cells/µL. One patient with severe pulmonary hypertension also received epoprostenol sodium by continuous intravenous infusion at a dose of 8 ng/kg per minute.

Response Criteria

Criteria for evaluating the hematologic response to induction therapy consisted of the following. A complete response was defined as a lack of detectable monoclonal protein in serum and urine samples by immunoelectrophoresis and immunofixation, as well as normalization of the bone marrow plasma cells (<5% plasma cells). A partial response was defined as a reduction of serum monoclonal protein by at least 50%. A decrease in serum monoclonal protein by 25% was considered a minor response. To qualify as a response, serum or urine M protein values had to be stable for at least 4 weeks. Relapse or progression was defined as an increase in serum monoclonal protein to greater than 25% above the lowest response level. To qualify as progression, that value must also be an absolute increase of at least 0.5 g/dL. In patients who achieved complete response, the detection of M protein by immunofixation, even if not accompanied by measurable changes, was considered progression. Skin responses were evaluated by serial tactile examination by a dermatologist and by photographs.

RESULTS

One heavily pretreated patient failed to mobilize enough stem cells to proceed to transplantation. She subsequently was successfully treated with thalidomide and was doing well at the last follow-up visit. Five patients underwent PBSCT. All patients were assessed for toxic reaction and response. The median time from initial symptoms until transplantation was 21 months (range, 7-36 months). All patients underwent detailed dermatologic examinations by a dermatologist, and skin biopsy specimens were obtained. All patients had an associated monoclonal protein, 4 had IgG, and 2 had IgGk. The M spike size ranged from 0.5 to 1.9 g/dL. Four patients had had prior systemic therapy, including high-dose corticosteroids (2 patients), combined melphalan and prednisone (3 patients), other alkylating agents (1 patient), thalidomide (2 patients), retinoids (3 patients), psoralen–UV-A (3 patients), plasmapheresis (1 patient), intravenous immunoglobulin (1 patient), and hydroxychloroquine sulfate (1 patient).

Extracutaneous manifestations included gastrointestinal dysmotility (3 patients); pulmonary complications, including obstructive lung disease (3 patients); cardiac involvement with severe pulmonary hypertension (1 patient); and neurologic involvement with grand mal seizures (2 patients). The presenting clinical information is summarized in Table 1.

TOXIC REACTIONS

All patients were initially treated as outpatients. Four were hospitalized, with the length of stay ranging from 1 to 10 days. The reasons for hospitalization included neutropenic fever (3 patients), diarrhea (2 patients), mucositis (1 patient), and atrial fibrillation (1 patient). Three patients had proven bacteremias, with blood cultures positive for Streptococcus viridans (1 patient) and Staphylococcus epidermidis (2 patients). All recovered with the use of appropriate intravenous antibiotics. All patients engrafted. The median time to achieve white blood cell counts greater than 500 cells/µL was 14 days (range, 12-17 days). There was no transplant-related mortality.

RESPONSES

All 5 patients were evaluable for responses. Hematologic responses were seen in 4 patients, including 2 complete responses and 2 partial responses. The fifth patient had a minor M spike drop (1.9-1.3 g/dL) but no improvement of skin. Improvement of skin involvement was seen in the other 4 patients even in the absence of hematologic complete responses. Softening of the skin was seen as early as day 6. The 4 responding patients had dramatic resolution by day 100. Skin nodules and nodular plaques disappeared (Figure). Four pa-
Patients subsequently had M spike relapses 19 to 27 months after PBSCT. Three patients developed skin relapses 14, 37, and 45 months after PBSCT. Two of the relapsed patients subsequently had skin responses to intravenous immunoglobulin. Improvements in extracutaneous manifestations were also seen. Three patients had improvement in gastrointestinal dysmotility, with stabilization of weight. Three had resolution of dyspnea. A patient who presented with grand mal seizures has had no further seizures for more than 46 months but is still taking antiseizure medications. The patient with pulmonary hypertension was able to be tapered off epoprostenol therapy by 2 months after transplantation, but pulmonary pressures as measured by echocardiography were unchanged at his day 100 evaluation. Responses are summarized in Table 2. The results of the assays for FLCs are summarized in Table 3.

### Table 2. Responses to High-Dose Chemotherapy With Peripheral Blood Stem Cell Transplantation (PBSCT)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Best M Spike</th>
<th>M Spike Relapse After PBSCT, mo</th>
<th>Skin Response</th>
<th>Skin Relapse After PBSCT, mo</th>
<th>Extracutaneous Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IF−</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>IF+</td>
<td>19</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>IF−</td>
<td>27</td>
<td>Yes</td>
<td>&gt;46</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>0.6 g/dL</td>
<td>14</td>
<td>Yes</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>1.3 g/dL</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: IF, immunofixation; NA, not available.

### Table 3. Results of Serum Free Light Chain (FLC) Assays

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pretransplantation</th>
<th>Posttransplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>κ FLC</td>
<td>λ FLC</td>
</tr>
<tr>
<td>1</td>
<td>0.17</td>
<td>0.27</td>
</tr>
<tr>
<td>2</td>
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<td>3.88</td>
</tr>
<tr>
<td>3</td>
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<td>2.13</td>
<td>1.32</td>
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<tr>
<td>6</td>
<td>0.23</td>
<td>1.43</td>
</tr>
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</table>

Current treatment for scleromyxedema usually is unsatisfactory, although there are reports of responses to corticosteroids and single alkylating agents, particularly melphalan. The fact that many patients have a poor response is reflected in the large number of treatments that have been tried. These include chemotherapeutic agents, such as the alkylators, methotrexate, cladribine, glucocorticoids, isotretinoin, interferon alfa, dimethyl sulfoxide, extracorporeal photochemotherapy, plasmapheresis, thalidomide, intravenous immunoglobulin, and psoralen–UV-A. In 1969, Feldman et al described a dramatic response to melphalan therapy, and a 1979 report on a series of 8 patients confirmed that melphalan therapy could be effective in some patients (4 patients had an excellent response). The toxic effect of melphalan is substantial, and in the largest series to date, Dinneen and Dicken reported on 17 patients who received melphalan therapy. Six (35%) of the patients died of treatment-related complications, 2 (12%) of acute leukemia and 4 (24%) of infectious complications. The mode of administration of melphalan (oral) may have affected the results. Twelve of the 17 patients had a response, but 8 of the responses were transient and limited to the skin. Feasel et al first reported remission of scleromyxedema following autologous stem cell transplantation in 2001.

An expanding body of literature suggests that PBSCT is effective in other serious low-grade plasma proliferative disorders, such as primary systemic amyloidosis and POEMS syndrome. In patients with myeloma who were undergoing autologous transplantation, Singhal et al showed that the probability of clearance of the monoclonal protein was 46.7% if the initial protein level was greater than 1 g/dL and 94.4% if it was 1 g/dL or less.

These considerations led us to offer high-dose chemotherapy with stem cell rescue to our patients. In addition, the mortality risk for autologous hematopoietic progenitor cell transplantation for multiple myeloma is less than 2%. Our patients have had favorable clinical and laboratory responses, as well as improved quality of life. Although our first patient received treatment with several alkylating agents, including melphalan, before stem cell harvest, we were able to obtain an adequate number of CD34+ cells to proceed with transplantation. We were unable to obtain enough stem cells to proceed with transplantation in a second heavily pretreated patient. This underscores that it is prudent to consider stem cell harvest before prolonged exposure to melphalan treatment. Alkylating agents can affect the quantity and quality of stem cell.
harvests. Unfortunately, this therapy did not prove to be curative for our 3 patients who have relapsed. However, the lack of response to other treatment modalities and the improvements in quality of life, skin involvement, and extracutaneous manifestations justify the use of high-dose chemotherapy in these patients.

The FLC is crucial in the pathogenesis of amyloidosis, light chain deposition disease, and light chain myeloma. The FLC assay can be used to monitor disease progression and response to therapy for these diseases. The role of the FLCs in the pathogenesis of scleromyxedema is less clear, but the present study raises some important questions. Unlike other plasma cell disorders, FLC levels were normal or only mildly abnormal in all patients before PBSCT. However, the FLC ratio was abnormal in 2 of the patients (patients 4 and 5) after PBSCT, including the patient with the shortest duration of remission and the patient who did not respond to PBSCT. Further studies of FLC values in patients with scleromyxedema are needed to clarify whether this assay will prove useful in predicting which patients are at risk of progression of the disease.

The role of the associated monoclonal protein in scleromyxedema has not been elucidated. It has been shown that the serum of patients with scleromyxedema stimulates fibroblast proliferation in vitro. The only patient (patient 5) who did not obtain at least a hematologic partial response also did not have improvement in his skin or extracutaneous involvement, suggesting an association between the monoclonal gammopathy and the pathogenesis of scleromyxedema. However, our patients achieved improvement in the skin whether or not they eradicated the monoclonal protein, and the reemergence of the monoclonal protein predated skin relapses in all patients by 1 to 2 years. It is assumed that scleromyxedema has a pathophysiologic basis associated with the monoclonal gammopathy. The lack of an obvious relationship between the level of decrease in monoclonal protein and serum FLCs raises the possibility that the beneficial effect of transplantation may be because of the immunosuppressive effect of the process. This is consistent with the responses reported with the use of intravenous immunoglobulin and corticosteroids. Because all our patients ultimately relapsed, it further raises the question of whether these patients would benefit from some type of maintenance immunosuppressive therapy after PBSCT.

Based on our experience, autologous hematopoietic progenitor cell transplantation should be considered for patients with scleromyxedema. Our cohort of patients is small, and this retrospective report is descriptive. Further work should be done to clarify the role of the FLC assay in this group of patients, the mechanism by which PBSCT benefits the patients, and whether there is a role for maintenance therapy in these patients.

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