Extracorporeal Photopheresis and Adjuvant Aerosolized Granulocyte-Macrophage Colony-Stimulating Factor for Sézary Syndrome

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Encouraged by preliminary phase 1 studies of aerosolized granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) in the treatment of patients with melanoma and other malignancies, we treated a 72-year-old patient with Sézary syndrome, using alternate-week cycles of aerosolized GM-CSF in combination with monthly cycles of extracorporeal photopheresis (ECP). Sézary syndrome, one of the more aggressive forms of cutaneous T-cell lymphoma, is a devastating and highly symptomatic form of non-Hodgkin lymphoma in which malignant clones of mature helper CD4 T cells, containing large, convoluted nuclei known as Sézary cells, circulate in the blood and infiltrate skin. Extracorporeal photopheresis, an immunomodulatory therapy, has become a primary treatment for patients with Sézary syndrome. This pheresis-based therapy combines psoralen and ultraviolet A radiation as systemic photochemotherapy to induce immune responses. However, the activity and efficacy of ECP vary considerably. To our knowledge this is the first patient with Sézary syndrome treated with adjuvant aerosolized GM-CSF combined with ECP. It produced clinical improvement and decreased the number of circulating Sézary cells in a previously ECP-refractory patient.

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ECP = extracorporeal photopheresis; GM-CSF = granulocyte-macrophage colony-stimulating factor

Cutaneous T-cell lymphoma represents a group of low-grade, non-Hodgkin lymphomas, including Sézary syndrome, mycosis fungoides, and their variants.1-3 Sézary syndrome, the leukemic and most aggressive subtype of cutaneous T-cell lymphoma, has a poor prognosis.1-2 Clinical features of Sézary syndrome include exfoliative erythroderma, pruritus, generalized lymphadenopathy, alopecia, onychodystrophy, palmoplantar hyperkeratosis, and ectropion.1-3 Various established as well as newer therapies are used to manage patients with Sézary syndrome, including extracorporeal photopheresis (ECP), interferon alfa, bexarotene, denileukin diftitox, and other chemotherapeutic agents such as the nucleoside analogues.3-5 The treatment of erythrodermic cutaneous T-cell lymphoma with ECP was first described by Edelson et al in 1987.5 Data demonstrating the efficacy of ECP in enhancing survival of patients with Sézary syndrome remain controversial.6-9 Reports indicate that patients with normal CD8 cell levels and diminished CD4/CD8 ratios at the initiation of therapy have a higher response rate.8 However, the mechanism of action of ECP has not been well characterized. The activity of a related modality of skin-targeted photochemotherapy, psoralen–ultraviolet A therapy, appears to be related to induction of apoptosis in human T lymphocytes.11

Our extensive experience with ECP in the treatment of Sézary syndrome has shown that therapy must typically be prolonged, with slow development of clinical responses. Control of the malignancy is often lost over time. Improved individual or combined therapies with low toxicity are urgently needed for Sézary syndrome. In this regard, immunoadjuvant agents, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), are increasingly being recognized for their ability to enhance the efficacy of various cancer immunotherapy regimens.12 Antigen-presenting cells are a functional class of dendritic cell that have a unique capacity for capturing, processing, and presenting antigens at sites of encounter and inducing a primary immune response after interaction with T lymphocytes. Antigen-presenting cells regulate antigen recognition by the immune system and determine whether a subsequent immune response is generated.13 A potent cytokine, GM-CSF has been shown to mature and expand the population of antigen-presenting cells.13-14 This cytokine has the potential for playing an important role as an immune adjuvant in vivo by reversing compromised immune responses that develop in Sézary syndrome and other hematologic malignancies. For example, there is clinical evidence of an effective immunoadjuvant role of GM-CSF in acute leukemias.15,16 In addition, GM-CSF, when given in combination with neoadjuvant chemotherapy, increases

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the dendritic cell function and improves survival in patients with locally advanced breast cancer and other locally advanced cancers.17,18 Use of GM-CSF in aerosolized form, a novel, less invasive route of administration, has shown promise in metastatic melanoma and other cancers.19 These observations encouraged us to use aerosolized GM-CSF in combination with ECP for treatment in Sézary syndrome when the lymphoid malignancy had progressed despite combined interferon alfa and ECP therapy. For this case report, institutional review board approval and informed consent of the patient were obtained.

REPORT OF A CASE
A 59-year-old man presented to the Department of Dermatology of the Mayo Clinic, Rochester, Minn, in January 1989 with a 1½-year history of chronic erythema and scaling of the skin. Physical examination revealed dry, generalized scaling and erythema of the face, abdomen, back, buttocks, and extremities, along with palmoplantar hyperkeratosis and bilateral inguinal lymphadenopathy. Lymph node and skin biopsy specimens were interpreted as cutaneous T-cell lymphoma. Analysis of peripheral blood smears showed an absolute Sézary cell count of more than 1.0 × 10⁹/L. Sézary syndrome was diagnosed, and the patient was given monthly cycles of ECP.

In April 1991, because of minimal clinical response and progression of symptoms, subcutaneous interferon alfa-2b, at a weekly dose of 15 million units, was added. Intractable weakness, nausea, and flulike symptoms forced discontinuation of interferon in April 1994 after 3 years of therapy. The ECP alone was continued on a monthly basis from April 1994 to June 2000. During this period, serial absolute Sézary cell counts ranged from 2.0 to 2.5 × 10⁹/L. However, the skin condition and symptoms eventually worsened to the extent that the patient became erythrodermic and was experiencing severe pruritus and depression (Figures 1 and 2). The absolute Sézary cell counts had also increased, averaging 3.2 × 10⁹/L over 6 months.

Although ECP treatment had provided partial control of the cutaneous T-cell lymphoma over the previous 11 years, additional therapy was indicated because of worsening disease. Aerosolized GM-CSF (sargramostim) on an alternate-week regimen, administered by nebulizer at 250 µg twice a day, was started. Monthly ECP therapy was continued. One month after beginning therapy with aerosolized GM-CSF, the patient experienced a blistering and erosive eruption on the left side of the chest, which extended posteriorly to the subscapular area. By reverse transcription polymerase chain reaction analysis of a skin specimen, herpes zoster was diagnosed and famciclovir was prescribed. Therapy with GM-CSF was withheld for 2 weeks.
The herpetic infection cleared rapidly, and GM-CSF was restarted.

Over the subsequent months, from July through November 2000, the patient’s erythema, ectropion, and hyperkeratosis improved (Figure 3). The absolute Sézary cell count had decreased to $0.30 \times 10^9/L$ by November 2000 (Figure 4). Therapy with GM-CSF was discontinued in November 2000 because the patient’s insurance company refused to reimburse expenses for GM-CSF. Five months later, without the GM-CSF aerosolized therapy but with continued monthly ECP treatments, the skin findings were stable, and the absolute Sézary cell count remained less than $1.0 \times 10^9/L$ (Figure 4).

**DISCUSSION**

Sézary syndrome is a debilitating, malignant T-cell lymphoproliferative disorder of CD4 T cells, which involves the skin, blood, and lymph nodes. It has been associated with a poor prognosis. Several newer therapeutic approaches to control Sézary syndrome have included bexarotene, denileukin diftitox, combination chemotherapy, and interferon alfa-2b. Unfortunately, these treatments have largely been palliative rather than curative.

Studies at the Mayo Clinic have demonstrated the utility of aerosolized GM-CSF in treating various cancers. Additional clinical observations of aerosolized GM-CSF in the treatment of melanoma by Markovic et al (unpublished data, April 2000) encouraged us to add aerosolized GM-CSF to ECP therapy for Sézary syndrome. GM-CSF is a pleiotropic cytokine having marked effects on dendritic cells, including induction of further development and maturation of antigen-presenting cells. Lim et al have shown that freshly isolated dendritic cells mature in short-term culture (24-36 hours) under the influence of GM-CSF. This cytokine stimulates the transition of cells with active protein antigen-processing capacity but weak T-cell-stimulating activity to potent immunostimulatory cells with less avid antigen-processing ability. This response is accompanied by a markedly enhanced capacity to induce proliferation and cytokine secretion by naive T cells. These effects of GM-CSF on dendritic cells target specific immunostimulatory mechanisms, which may prove clinically useful in maximizing host defenses against malignancy.

Other cytokines that are reportedly active in the treatment of cutaneous T-cell lymphoma include interferon alfa, interleukin 2, and interleukin 12. In a clinical study of lymphoma patients, Chaperot et al, as part of a vaccine therapeutic strategy, demonstrated the efficiency of antigen-presenting cells in endocytosing, processing, and presenting lymphoma-associated proteins. They found that both dendritic cells and macrophages can be efficiently harvested and differentiated in large numbers from lymphoma patients despite the compromising effects of the disease and previous therapy. Dendritic cells and macrophage-like cells were differentiated from circulating monocytes in the presence of GM-CSF and interleukin 13 or with GM-CSF alone.

Studies have also demonstrated the activity of GM-CSF in potently activating lung dendritic cells. Wang et al showed that transgenic expression of GM-CSF in lung strongly induces differentiation and activation of a novel antigen-presenting cell in the lungs of mice. They showed that GM-CSF acts primarily on macrophages during pulmonary immune responses. Suda et al observed that lung dendritic cells cultured with GM-CSF represented a source by which these cells may be readily recruited not only to replenish normal mucosal dendritic cells but also to participate in inflammatory reactions occurring in the lung.

In the present case, addition of aerosolized GM-CSF to ECP therapy may have contributed to improvement in the patient’s clinical status and decreased the levels of circulating Sézary cells. These effects may have occurred via the local activation of lung antigen-presenting cells by aerosolized GM-CSF and the induction or enhancement of immune recognition directed against the malignant T-cell population. We postulate that an increase in the CD8 cell population, composed of cytotoxic T lymphocytes, is directed at the malignant CD4 cell population and may be a principal immune response by which GM-CSF acts. Less likely is the possibility that GM-CSF directly induces...
apoptosis or cessation of proliferation of the malignant CD4 cell population.

Extracorporeal photopheresis may further contribute to the combined therapeutic activity of GM-CSF by directly inducing apoptosis of malignant T cells, as reported recently by Osella-Abate et al. Apoptosis of CD4 malignant cells may serve as a more potent source of antigen for processing by lung antigen-presenting cells. We postulate that incorporating GM-CSF in the treatment regimen enhances the therapeutic index of ECP and the antigen-presenting cell response within the lung. We believe that the systemically activated cytotoxic T lymphocytes target the circulating CD4 malignant T-cell population. Either as monotherapy or in conjunction with specific cytokines, ECP may be inducing similar immune responses. However, aerosolized GM-CSF may be a preferred cytokine adjuvant and route for the activation of lung dendritic cells. The entire blood compartment circulates through the capillary bed of the lungs, where GM-CSF can be delivered easily to pulmonary dendritic cells with virtually no toxic effects. Although our experience is limited to a single case, further clinical studies of aerosolized GM-CSF, whether in conjunction with ECP, as cytokine monotherapy, or as a component of a vaccine for cutaneous T-cell lymphoma, are warranted.

REFERENCES