

Alemtuzumab as initial therapy for Sézary syndrome: A report of 2 cases



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INTRODUCTION

The approval of mogamulizumab, an anticytokine receptor 4 antibody, by the Food and Drug Administration for cutaneous T-cell lymphoma and Sézary syndrome in 2018 brought cutaneous T-cell lymphoma into the era of targeted therapy. However, alemtuzumab, an anti-CD52 monoclonal antibody approved in the United States for the treatment of chronic lymphocytic leukemia and multiple sclerosis, has been used off label in advanced cutaneous lymphomas since 2003. CD52⁺ T-cells are a common phenotype in Sézary syndrome, but alemtuzumab's use for this disease is off label and current guidelines recommend it only for relapsed or refractory disease.¹ Although the use of alemtuzumab in such cases is well described, there are few reports describing its use as initial therapy in Sézary syndrome. Alinari et al² treated 1 patient with alemtuzumab without any previous therapy, who attained greater than 15 months of disease-free survival. Kho et al³ reported a case of a 56-year-old man who received alemtuzumab as initial therapy and had a complete response at 30 weeks (including significant improvement in leonine facies) and no observed toxicity. Bernengo et al⁴ used low-dose subcutaneous alemtuzumab in 3 treatment-naive patients, with minimal toxicity and an overall response duration of 12 months. Only 1 retrospective series studying alemtuzumab in this patient population has included patients without pretreatment,⁵ but the number of treatment-naive patients was not noted. In accordance with these reports, we treated 2 patients with alemtuzumab before administering any other systemic agents.

CASE REPORTS

Case 1

A 74-year-old man with a history of chronic kidney disease caused by membranoproliferative glomerulonephritis treated with azathioprine presented with erythroderma and intense pruritus (Fig 1). He underwent 4 skin biopsies, which demonstrated mild spongiotic dermatitis with dense CD3⁺ lymphocytic inflammation (Figs 2 and 3) and T-cell receptor beta clonality. Flow cytometry on blood was obtained, which showed that 96% of circulating T lymphocytes were CD52⁺ (Table I), and clonality for the T-cell receptor beta was detected. Biopsy of an enlarged inguinal lymph node was negative for malignant cells. He received an initial staging level of T4N0M0B2 (International Society for Cutaneous Lymphomas and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer, stage IVA₁). Because of the presence of proteinuric chronic kidney disease, methotrexate, histone deacetylase inhibitors, and systemic retinoids were avoided and the patient was treated with alemtuzumab 10 mg intravenously 3 times per week, along with trimethoprim-sulfamethoxazole and acyclovir for infection prophylaxis. He completed 8 weeks of alemtuzumab with a short treatment interruption because of asymptomatic cytomegalovirus reactivation and eventual resolution of viremia. Otherwise, alemtuzumab was well tolerated and he had complete clearance of his skin and blood by Olsen criteria.⁶ After 12 months of follow-up, his skin remained clear, with only a sparse population of abnormal T cells detectable in blood (Table I).

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Fig 1. Erythroderma with light scaling in case 1 on initial presentation.

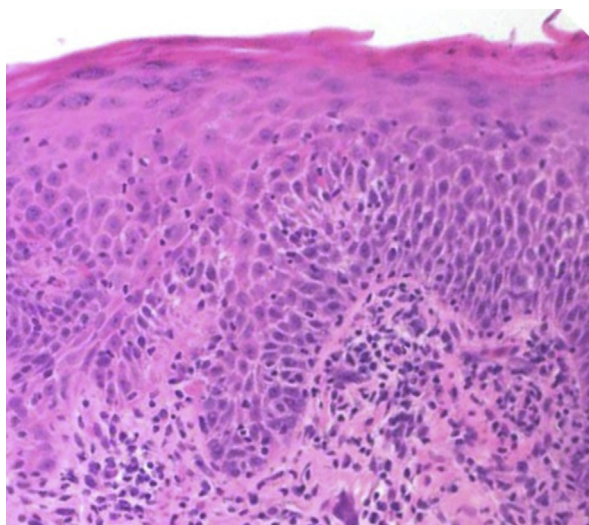


Fig 2. Skin biopsy from case 1 showing mild spongiosis with lymphocytic inflammation and lymphocytes in the epidermis.

Case 2

A 55-year-old man was referred for progressive erythroderma associated with scaling and pruritus that was unresponsive to 3 months of psoralen plus ultraviolet A treatment. Skin biopsy revealed cutaneous T-cell lymphoma and T-cell receptor gamma clonality. Flow cytometry was obtained and 81% of circulating T lymphocytes were found to be CD52⁺ (Table 1); clonality of the T-cell receptor gamma receptor was detected. Initial staging was again T4N0M0B2 (stage IVA₁) and

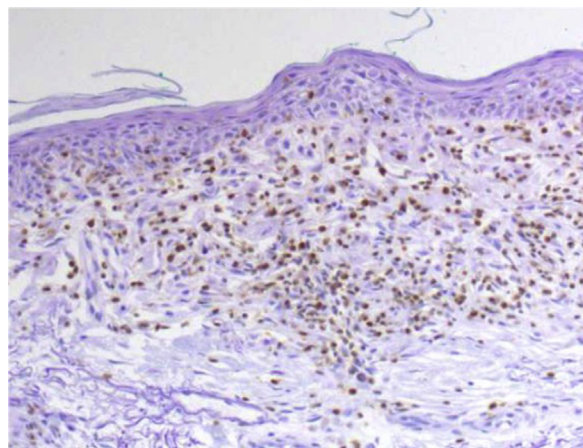


Fig 3. CD3 stain showing predominantly T-cell infiltrate with epidermotropism of smaller lymphocytes.

treatments targeting the blood component were recommended. He was offered extracorporeal photopheresis plus conventional first-line agents or alemtuzumab monotherapy, and he opted for treatment with alemtuzumab at a center closer to his home because of the distance he would have had to travel to receive extracorporeal photopheresis at our institution. He underwent 16 weeks of treatment with 10 mg intravenous alemtuzumab 3 times per week, with the same infection prophylaxis. There was prompt resolution of his erythroderma and clearance of the immunophenotypically abnormal cells in blood (Table 1). He had complete response based on Olsen criteria. He developed scaly, erythematous skin plaques 18 months later that showed relapsed cutaneous T-cell lymphoma on biopsy. His disease was managed with total skin electron beam therapy and eventually recurred in his blood 2 years after treatment; he was referred for allogeneic hematopoietic stem cell transplantation.

DISCUSSION

Sézary syndrome is a T-cell lymphoma that is difficult to treat and is associated with frequent relapses. Commonly used systemic treatments include bexarotene, interferon alfa, histone deacetylase inhibitors (such as vorinostat and romidepsin), methotrexate, extracorporeal photopheresis, and, more recently, mogamulizumab. Alemtuzumab has been reported as a successful initial treatment for Sézary syndrome in case reports and small series, but the initial studies and more recent trials have enrolled only patients with relapsed or refractory disease.²⁻⁵ In relapsed advanced cutaneous T-cell lymphoma and Sézary syndrome, patients who received 1 or 2 agents before alemtuzumab had a better response than those who received 3 or more

Table 1. Patient characteristics, initial flow cytometry, posttreatment flow cytometry, and treatment course

Case	Age, sex	Pretreatment			Posttreatment			Dose, duration	Response, duration	Complications	Outcome	
		CD4 ⁺ CD8	CD4 ⁺ CD7 ⁻ (%)	CD4 ⁺ CD26 ⁻ (%)	CD4 ⁺ CD52 ⁺ (%)	CD4 ⁺ CD7 ⁻	CD4 ⁺ CD26 ⁻					CD4 ⁺ CD52 ⁺ (%)
1	74, M	32	5566 (96)	4175 (69)	5808 (96)	10	7	0	10 mg IV TIW 8 wk	Complete, 12 mo	Asymptomatic CMV viremia	In remission
2	55, M	23	2752 (86)	960 (30)	2592 (81)	85	63	6 (2)	10 mg IV TIW 16 wk	Complete, 18 mo	Relapsed skin disease	HSCT

CMV, Cytomegalovirus; HSCT, hematopoietic stem cell transplant; IV, intravenously; M, man; TIW, 3 times per week.

agents (80% vs 23% overall response).⁷ In a series of 6 pretreated patients, the only one who failed to respond had dim CD52 positivity on flow cytometry.⁸ Additionally, in a patient treated with alemtuzumab, an acquired mutation in the anchoring protein for CD52, phosphatidylinositol glycan class A, caused disease relapse.⁹ Together, these reports provided the rationale for targeting CD52 in the 2 patients we treated.

Alemtuzumab has been used for many years in patients with multiple sclerosis and chronic lymphocytic leukemia. It is given as a 12-mg daily dose for 3 to 5 days every 12 months for multiple sclerosis and in escalating doses (up to 30 mg) 3 times weekly for up to 12 weeks for chronic lymphocytic leukemia. For off-label use in Sézary syndrome, a dosing schedule similar to that for chronic lymphocytic leukemia has been advocated, with doses as high as 30 mg per infusion. Important toxicities of alemtuzumab in these settings include infusion reactions, infections (mainly herpesvirus infections), autoimmune endocrinopathies, immunomediated thrombocytopenia, and anti-basement membrane disease (Goodpasture syndrome), with duration of treatment playing a role in adverse effect incidence.¹⁰ Low-dose subcutaneous alemtuzumab (less than 10 mg per injection) has been used successfully in relapsed Sézary syndrome, with no toxicity reported.⁴ The generally short courses of therapy needed to obtain remission may avert some of the toxicity observed in more chronic conditions in which alemtuzumab is used, such as multiple sclerosis.

Both patients presented before approval of mogamulizumab for Sézary syndrome, and we elected to treat them with alemtuzumab because of nearly uniform CD52⁺ of the circulating malignant cells on flow cytometry. We found that we did not need to exceed 10 mg per dose according to the rapid clinical responses noted in both cases. Intravenous administration was chosen in accordance with our usual practice in chronic lymphocytic leukemia, but subcutaneous injection also appears to be effective,^{2,11} and optimizing administration route is an area of active research. Similar to what has been described in the literature, both patients we treated with alemtuzumab had a favorable clinical course.

As with many descriptions of off-label therapeutic interventions, there may be a tendency for publication bias. Herein we report 2 cases of Sézary syndrome in which alemtuzumab was used as the initial systemic agent, with both patients attaining complete response by Olsen criteria and mild toxicities. A review of the literature demonstrates a paucity of such cases.

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