A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas

Gunilla Enblad, Hans Hagberg, Martin Erlanson, Jeanette Lundin, Anja Porwit MacDonald, Roland Repp, Johannes Schetelig, Gernot Seipelt, and Anders Österborg

Patients with peripheral T-cell lymphomas (PTLs) have an extremely poor prognosis when relapsed or refractory to conventional chemotherapy. We have studied alemtuzumab, a humanized anti-CD52 monoclonal antibody, as therapy for patients with heavily pretreated and refractory PTL. Fourteen patients entered the study. All had clinical stage III or IV disease. Patients received a rapidly escalating dosage of alemtuzumab during the first week and, thereafter, 30 mg intravenously 3 times per week for a maximum of 12 weeks. Trimethoprim/sulphamethoxazole and valaciclovir prophylaxis was given to all patients. The overall response rate was 36% (5 of 14). Three patients achieved a complete remission (CR) and 2 patients a partial remission. The durations of the CRs were 2, 6, and 12 months, respectively. Toxicity included cytomegalovirus reactivation in 6 patients, which was successfully treated with ganciclovir or foscarnet; pulmonary aspergillosis in 2 patients; and pancytopenia in 4 patients. Epstein-Barr virus–related hemophagocytosis was observed in 2 patients. Five patients died of causes related to the treatment, in combination with advanced disease. We conclude that alemtuzumab is active when used in patients with advanced, heavily pretreated PTL, although it is associated with significant hematologic toxicity and infectious complications. Further studies are warranted in younger patients and patients with less advanced disease. (Blood. 2004;103:2920-2924)

Introduction

T-cell lymphomas are rare and account for only 5% to 10% of all malignant lymphomas in the Western population.[1] According to the World Health Organization (WHO) histologic classification, the mature T-cell lymphomas can be divided into leukemic, cutaneous, "other extranodal," and nodal. The other extranodal (nasal type, enteropathy type, hepatosplenic, and subcutaneous panniculitis subgroups), together with the nodal (angioimmunoblastic, peripheral T-cell lymphoma unspecified, and anaplastic large cell lymphoma subgroups), are often termed peripheral T-cell lymphoma (PTL).[1] PTLs are clinically aggressive and have a worse prognosis than high-grade malignant B-cell lymphomas; fewer than 30% of patients are expected to be cured with anthracycline-containing combination chemotherapy.[1-4] At relapse, or if the disease is primary chemotherapy refractory, the prognosis is extremely poor. To improve the prognosis, high-dose regimens have been explored,[5] with promising results in selected patients; however, to date, no definite agreements have been reached on how to treat this patient group. There is, therefore, a great unmet need for novel treatment modalities in patients with PTL.

Alemtuzumab (MabCampath, Campath; Ilex Pharmaceuticals, San Antonio, TX) is a humanized immunoglobulin G_1 (IgG_1; CDR grafted) anti-CD52 monoclonal antibody that binds to the cell membrane of more than 95% of all normal human blood lymphocytes, as well as to most B- and T-cell lymphomas.[6] In addition to its documented effects in B-cell chronic lymphocytic leukemia (B-CLL),[7,8] alemtuzumab has demonstrated a promising clinical effect in patients with T-cell prolymphocytic leukemia (T-PLL)[9] and in mycosis fungoides/Sezary syndrome (MF/SS).[10] Malignant T cells appear to express extraordinarily high numbers of CD52 cell surface molecules (approximately 500 000 molecules per lymphocyte).[11] Thus, T-cell lymphomas, including PTLs, may be particularly suitable for therapy with alemtuzumab.

The aim of the present study was to determine the safety and efficacy of alemtuzumab therapy for patients with relapsed and chemotherapy-refractory PTL. We show, for the first time, that alemtuzumab has considerable antitumor activity in advanced PTL but is associated with significant toxicity in such patients.

Patients and methods

Study design

A phase 2, open-labeled study was conducted in 7 centers in Sweden and Germany. This study was approved by each institution's ethics committee and the Medical Products' Agency. Written informed consent was provided according to the Declaration of Helsinki. The objectives of the study were as follows: to determine the response rate with alemtuzumab in patients with relapsed or chemotherapy-refractory PTL; to evaluate the safety

From the Department of Oncology, Uppsala University Hospital, Uppsala, Sweden; Umeå University Hospital, Umeå, Sweden; Departments of Hematology/Oncology and Pathology, Karolinska Hospital, Stockholm, Sweden; Department of Medicine, University of Erlangen, Erlangen, Germany; Department of Medicine, University Hospital Carl Gustav Carcus, Dresden, Germany; and Department of Hematology/Oncology, University Hospital, Frankfurt, Germany.

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Reprints: Gunilla Enblad, Department of Oncology, Uppsala University Hospital, S-751 85 Uppsala, Sweden; e-mail: gunilla.enblad@onkologi.uu.se.

profile of alemtuzumab in this population; and to determine disease-free and overall survival. Patients eligible for the study were aged 18 to 75 years, with a confirmed diagnosis of PTL unspecified, angioimmunoblastic T-cell lymphoma, extranodal T-cell lymphoma (nasal type), enteropathy-type T-cell lymphoma, or anaplastic large cell lymphoma (noncutaneous). Patients were required to have failed or relapsed after treatment with an anthracycline-containing regimen and to be ineligible for high-dose chemotherapy. Failure was defined as lack of a complete remission (CR) or signs of progressive disease (PD). Patients should have received no more than 3 previous systemic therapy regimens and have a WHO performance status of 2 or less and a life expectancy of at least 3 months. Creatinine and bilirubin levels should be no higher than twice the upper normal limit. The exclusion criteria were as follows: previously untreated PTL; cutaneous anaplastic large cell lymphoma; HIV positivity; active ongoing infection, which was not under control with antibiotics; a past history of anaphylaxis following exposure to rat- or mouse-derived monoclonal antibodies; fewer than 4 weeks since prior chemotherapy; previous therapy with alemtuzumab; other severe concurrent diseases or mental disorders; or eligibility for high-dose chemotherapy.

Study treatment

Alemtuzumab (ILEX Pharmaceuticals, San Antonio, TX) was diluted in 100 mL of 0.9% normal saline and administered over 2 hours through an intravenous infusion line containing a 0.22-μm filter. A rapidly escalating initial dosage regimen was used: 3 mg on day 1; 10 mg on day 3; followed by 30 mg, 3 times a week, for a maximum of 12 weeks, as described previously.[10] Patients received 1 g paracetamol orally, antihistamines (clemastine 2 mg intravenously), and betamethasone 8 mg intravenously 30 minutes prior to the first alemtuzumab infusion and at each dosage escalation. Betamethasone was withdrawn after the first week of treatment. Trimethoprim/sulphamethoxazole, twice daily, 3 times per week, and valaciclovir, 500 mg twice daily, were administered starting on day 8 and were continued during the study and up to a minimum of 2 months following the discontinuation of alemtuzumab therapy. Allopurinol, 300 mg per day orally, was given to all patients from day 1 to day 28. Alemtuzumab therapy was stopped in the event of patients achieving a CR or fulfilling the criteria for a PD. Therapy was temporarily discontinued in the event of grade IV hematologic toxicity (platelet count $< 25 \times 10^9$/L and absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L) and restarted on recovery of platelet count to greater than 50×10^9/L and ANC to greater than 1.0×10^9/L. If treatment was interrupted for longer than 7 days, the dosage was reinitiated at 3 mg or 10 mg.

Safety assessments

Patients were monitored continuously for alemtuzumab-related toxicity. Side effects were graded according to the WHO toxicity criteria. Blood counts and a differential were analyzed once weekly.

Disease evaluation

The extent of lymphoma was evaluated within 10 days prior to the start of treatment. Patients underwent a physical examination with bidimensional measurement of enlarged lymph nodes; a chest X-ray; a chest and abdominal computed tomography scan; bone marrow aspiration/trephine biopsy; and routine laboratory tests, including blood counts, differential, liver function tests, and serum protein and electrolyte measurements.

Assessment of response was performed after 6 weeks, at the completion of therapy, and thereafter every third month during follow-up. CR was defined as the disappearance of all known disease, and partial remission (PR) was defined as more than a 50% reduction in tumor size.[5]

Bone marrow biopsies and Epstein-Barr virus detection

In 2 cases of hemophagocytosis (see "Hematologic toxicity"), an Epstein-Barr virus (EBV) early RNA (EBER) in situ hybridization (ISH) of bone marrow samples was performed. Bone marrow biopsies were formalin fixed and decalcified by Heidenhein-SuSa fixative. Sections (4-5 μm) were cut and stained with Giemsa, hematoxylin-eosin, Prussian blue, or Gordon-Sweet reticulin. Biopsies were evaluated for overall cellularity, representation and maturation of hematopoietic lineages, and the presence of lymphoma infiltrates. The presence of EBV in biopsies was investigated by ISH for EBER, using an INFORM EBER Kit and a Benchmark IHC/ISH Staining Module (Ventana Medical Systems, Tucson, AZ).

Results

Patient population

Fourteen patients were included in the study. Their clinical characteristics are presented in Table 1. All patients had clinical stage III or IV disease and were heavily pretreated with no response or PD following short remissions on the previous therapy. All but one patient had received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), or a similar regimen, as first-line therapy.

Table 1. Patient characteristics

Patient no.	Age, y	Sex	PTL subtype	No. of previous regimens	Response to previous therapy*	Clinical stage	Baseline: WBC count, $\times 10^9$/L	Baseline: Lymphocyte count, $\times 10^9$/L
1	60	M	PTLu	3	CR (2 mo)	IIIA	9.6	0.9
2	70	M	Angio	1	PD	IVA	4.7	1.1
3	61	F	PTLu	2	PD	IVA	4.6	1.0
4	65	M	AILD	1	PD	IIIB	3.6	1.1
5	53	F	AILD	2	CR (3 mo)	IVB	4.7	0.2
6	79	M	PTLu	3	SD	IVA	6.0	1.5
7	59	M	PTLu	1	PR (1 mo)	IVB	25.2	2.3
8	57	M	PTLu	1	PR (2 mo)	IVA	65.0	63.7†
9	62	M	Angio	2	PD	IIIA	17.8	0.9
10	65	M	PTLu	3	PD	IVA	1.3	0.6
11	57	M	PTLu	2	PR (8 mo)	IVA	4.6	1.0
12	78	M	PTLu	3	SD	IIIB	6.6	0.8
13	57	M	PTLu	2	PD	IVA	6.4	0.9
14	58	M	PTLu	4	PR (3 mo)	IVA	6.0	0.1

WBC indicates white blood cell; M, male; PTLu, peripheral lymphoma unspecified; Angio, angiocentric T-cell lymphoma; F, female; and AILD, angioimmunoblastic lymphoma.

*The number in brackets indicates the duration of response (months) to previous therapy.

†Lymphoma cells present in the blood of this patient.

Eight patients (57%) had received second-line combination chemotherapy with MIME (mitoguazone, ifosfamide, methotrexate, etoposide); Dexa-BEAM (dexamethasone, BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea], etoposide, ara-C, melphalan); or similar treatment, and 4 patients had also received fludarabine phosphate. Splenectomy had been performed in 3 patients, and 6 patients had also received radiotherapy or single-agent chlorambucil or cyclophosphamide as palliation. Two patients were older than 75 years of age (78 and 79 years, respectively) and one patient had received 4 previous regimens. These patients were included due to an urgent need for therapy and a lack of alternative treatment options (refractory disease).

Dosing

The median treatment time was 6 weeks (range, 3-11 weeks), and the median cumulative dose was 493 mg (range, 253-763 mg). Only one patient completed the planned 12 weeks of treatment. The remaining patients were withdrawn due to achievement of a CR (n = 3), toxicity, and/or PD (n = 10) after a median of 5 weeks (range, 3-11 weeks).

Response to alemtuzumab

CR was achieved in 3 patients (nos. 1, 7, and 8), and PR was achieved in 2 patients (nos. 6 and 9), giving an overall response rate of 36% (5 of 14 patients). The durations of the CRs were 2, 6, and 12 months, respectively. Four patients had stable disease (SD) and 5 patients had PD during alemtuzumab treatment.

Adverse events

Infusion-related adverse events. Infusion-related adverse events were reported in 9 of 14 patients. The most common events were shivers and chills during the first week, which occurred in 7 patients. Hypotension occurred in 2 patients, dyspnea in 2 patients, and urticaria with bronchospasm in one patient. These were confined to the first infusion(s) and were mainly mild or moderate in severity. No grade IV reactions were observed. After the first week, almost all infusion-related side effects disappeared.

Hematologic toxicity. At study entry, all but one patient had a normal neutrophil count. Hemoglobin values and/or platelet counts were below normal in 8 and 4 patients, respectively. The maximum increases (vs baseline) in hematologic toxicity are presented in Table 2. Pancytopenia occurred in 4 patients (nos. 3, 5, 9, and 12). In one patient (no. 9), the pancytopenia resolved within 2 weeks without treatment. In one patient (no. 12), the pancytopenia was a contributing factor in the patient's death, which resulted from aspergillosis, despite granulocyte-colony stimulating factor (G-CSF) treatment. Two patients (nos. 3 and 5) developed hemophagocytosis syndrome, a condition associated with PTL. At the time of developing hemophagocytosis, the patients had received 5 and 10 weeks of alemtuzumab treatment, respectively. For one of these patients (no. 3), SD of the lymphoma was observed, and the condition did not resolve despite treatment with high-dose gammaglobulin and corticosteroids. The patient died 2 months after starting this course of treatment. For the other patient (no. 5), evaluation of the lymphoma demonstrated PD. The treatment was changed to MIME chemotherapy and the hemophagocytosis was resolved. In both cases, bone marrow biopsies showed hypoplastic/aplastic marrow, with a relative increase in the level of phagocytic histiocytes. EBER ISH of the bone marrow demonstrated several mononuclear cells with nuclear positivity, confirming reactivation of an EBV infection. Simultaneously stained biopsies taken during the period before alemtuzumab treatment showed only single positive cells.

Table 2. Maximum increase in hematologic toxicity compared with baseline according to WHO toxicity grading

Patient no.	Leukocyte count	Neutrophil count	Hemoglobin level	Platelet count
1	3	2	0	0
2	1	0	0	0
3	4	3	1	2
4	1	1	0	3
5	4	4	4	3
6	2	0	0	0
7	0	0	1	0
8	4	1	0	0
9	2	1	1	0
10	2	4	0	0
11	3	1	1	0
12	3	2	0	2
13	1	—	1	1
14	0	—	0	1
Mean value	2.1	1.6	0.6	0.9

— indicates not measured.

Infectious complications. Cytomegalovirus (CMV) reactivation, diagnosed by a positive polymerase chain reaction (PCR) analysis, occurred in 5 patients after a median of 5 weeks (range, 3-7 weeks). In a sixth patient (no. 5), CMV reactivation occurred after the end of alemtuzumab therapy and during chemotherapy. Two of the 6 patients presented with fever only, and 4 patients had signs of pneumonitis. CMV infections were treated with ganciclovir or foscarnet and were resolved in all patients. One patient (no. 6) in PR died from an unknown pulmonary infection, which occurred 7 weeks after the onset of alemtuzumab therapy. At autopsy, a miliary tuberculosis was diagnosed. One patient (no. 9), who was in PR following 3 weeks of alemtuzumab treatment, died of a generalized herpes zoster infection, which occurred 4 months after the end of alemtuzumab treatment and 2 months after the cessation of valaciclovir prophylaxis. Two patients (nos. 12 and 14) developed pulmonary aspergillosis after 6 and 5 weeks of alemtuzumab treatment, respectively. In one patient (no. 12), this occurred in relation to pancytopenia (see "Hematologic toxicity"). Both patients died of the infection in combination with progressive lymphoma.

Taking the hematologic and infectious adverse events into account, the study was closed after 14 of the planned 25 patients had been enrolled. The safety evaluation demonstrated that 5 patients (nos. 3, 6, 9, 12, and 14) died from serious adverse events that were considered to be causally related to the study drug in combination with advanced, heavily pretreated PTL.

Discussion

Patients with chemotherapy-refractory or relapsed PTL have an extremely poor prognosis, with rapidly progressive disease despite treatment.[5] In this study, clinical responses to alemtuzumab were observed in more than one third (5 of 14, 36%) of patients with advanced PTL. Responses were obtained at all tumor sites, including lymph nodes, a tumor location which, in patients with B-cell lymphomas, has previously been reported to be less responsive to alemtuzumab therapy.[12] The antitumor activity observed in this study is promising, considering the relatively short average alemtuzumab treatment period. The duration of the remissions is also promising, with one patient remaining in unmaintained CR for 12 months and another for 6 months.

Mild or moderate first-dose, infusion-related side effects were observed in most patients, despite the use of corticosteroid prophylaxis. The role of corticosteroids in the prevention of such side effects cannot be determined by the present study, even though corticosteroids are often used successfully to treat severe “flulike,” infusion-related side effects during alemtuzumab therapy.[10]

The main problem in this study was the high rate of opportunistic infections, with 5 patients dying from infectious complications. However, this was not considered to be related to prior exposure to purine analog therapy, as only one of these 5 patients had previously received fludarabine phosphate. It should be noted that advanced T-cell lymphoma, in combination with previous treatment, caused severe immunosuppression in most patients even before the initiation of alemtuzumab therapy. Alemtuzumab is known to contribute further to such immunosuppression, mainly by depleting normal CD4 and CD8 T lymphocytes.[8,13] An increased risk of infectious complications during alemtuzumab therapy has previously been observed in other T-cell malignancies, such as T-PLL and MF/SS.[9,10] As shown in this study, patients with relapsed and refractory PTL may be at particularly high risk of developing opportunistic and other severe infections during alemtuzumab therapy, probably due to pre-existing suppression of T-cell functions, as a consequence of advanced disease and previous treatments. The increased risk induced by alemtuzumab is reflected by the high proportion of CMV reactivation (6 of 14 patients) observed in the present study, which appears to be higher than that observed in MF/SS and B-CLL.[10] In addition, the risk of CMV pneumonitis (ie, not only fever) appeared to be higher in this study compared with that observed in B-CLL and MF/SS.[7,10] Thus, careful monitoring of CMV (and possibly other potential pathogenic viruses) by repeated PCR analyses might be considered, to allow early medical intervention in such high-risk patients. In this study, the CMV infections were treated with ganciclovir or foscarnet and were resolved in all patients.

Hematologic toxicity was more pronounced than in previous alemtuzumab studies in B-CLL, T-PLL, and MF/SS. Hematologic toxicity was also higher than that expected for PTL patients not treated with alemtuzumab. This toxicity, in combination with the high proportion of severe infections, resulted in the decision to terminate the study early (despite an apparently high antitumor activity of alemtuzumab).

Two cases of hemophagocytosis were observed in our study, a higher incidence than that expected for PTL patients not treated with alemtuzumab. Hemophagocytosis has previously been described in PTL and can occur at diagnosis, during treatment, and at relapse, but also in remission.[14] Reactivation of an EBV infection may be the causative agent of most described cases.[14,15] A large proportion of PTL in immunocompetent patients is EBV related in Western Europe,[16] but it is unknown whether the virus-infected lymphoma cells start the process or if a latent EBV infection per se is a risk factor. The background of hemophagocytosis in PTL has not been entirely elucidated, since other EBV-positive lymphomas (ie, Hodgkin lymphoma or Burkitt lymphoma) are not associated with an increased risk of hemophagocytosis. Also, because patients with B-CLL and MF/SS treated with alemtuzumab have not been reported to develop hemophagocytosis, despite the immunosuppression induced by previous therapy, it is unlikely that the hemophagocytosis observed in this study is attributable to alemtuzumab therapy only.[13] It is possible that T-cell depletion by alemtuzumab resulted in EBV reactivation; however, this is highly speculative.

Two additional patients developed pancytopenia without signs of hemophagocytosis, the cause of which is unclear. This pancytopenia was unexpected, since hematopoietic stem cells ($CD34^+$) do not express CD52.[17] Notably, pancytopenia has previously been observed in occasional patients with T-PLL treated with alemtuzumab,[9] and delayed-onset neutropenia has been reported after rituximab therapy.[18]

In conclusion, this pilot study indicates that alemtuzumab may have high antitumor activity in PTL. The rate of remissions in this heavily pretreated, poor-prognosis group of patients is promising. However, the infectious and hematologic toxicity observed was unacceptably high, leading to an early closure of the study. Therefore, we recommend, at this point, that alemtuzumab should not be used to treat PTL patients unless they are involved in carefully designed clinical trials. Further studies on alemtuzumab are warranted, given its high activity in these relapsed/refractory patients. Novel therapeutic tools are under development, which may help to overcome the problems caused by a functionally impaired T-cell system and reduce the risk of severe infections in patients such as those reported here. As described by Thompson et al,[19] normal T cells may be activated and expanded in vitro using antibodies to CD3 and CD28 (immobilized on magnetic beads) and then propagated in vivo (Xcellerated T Cells; Xcite Therapies, Seattle, WA). Alternatively, antibody therapy may be adopted in vivo using superagonist CD28-specific antibodies, which in the murine model expanded both CD4 and CD8 T cells while maintaining a diverse T-cell receptor repertoire.[20] Alemtuzumab treatment, in combination with the emerging availability of technologies that help restore T-cell functions and numbers, may hopefully enhance the safety of CD52-targeted therapy in forthcoming clinical trials. Alternatively, lower dosages of alemtuzumab could be explored to improve the safety of alemtuzumab therapy in PTL patients. However, data from the study of autoimmune disorders indicate that $CD4^+$ T cells can be severely depleted for long periods of time, despite the administration of alemtuzumab at very low doses.[21] Further studies with alemtuzumab in PTL are warranted in patients with less advanced disease and earlier in the disease course. The safety and efficacy of alemtuzumab as a component of first-line therapy for PTL also needs to be investigated.

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