Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL)

Jeanette Lundin, Eva Kimby, Magnus Björkholm, Per-Anders Broliden, Fredrik Celsing, Viktoria Hjalmar, Lars Möllgård, Peppy Rebello, Geoff Hale, Herman Waldmann, Håkan Mellstedt, and Anders Österborg

This phase II study determined the efficacy and safety of alemtuzumab, a humanized anti-CD52 monoclonal antibody, delivered subcutaneously as first-line therapy, over a prolonged treatment period of 18 weeks in 41 patients with symptomatic B-cell chronic lymphocytic leukemia (B-CLL). Injections were administered subcutaneously 3 times per week, from week 2 to 3 onward. An overall response rate (OR) of 87% (95% CI, 76%-98%; complete remission [CR], 19%; partial remission [PR], 68%) was achieved in 38 evaluable patients (81% of intent-to-treat population). CLL cells were cleared from blood in 95% patients in a median time of 21 days. CR or nodular PR in the bone marrow was achieved in 66% of the patients and most patients achieved this after 18 weeks of treatment. An 87% OR (29% CR) was achieved in the lymph nodes. The median time to treatment failure has not yet been reached (18+ months; range, 8-44+ months). Transient injection site skin reactions were seen in 90% of patients. Rigor, rash, nausea, dyspnea, and hypotension were rare or absent. Transient grade IV neutropenia developed in 21% of the patients. Infections were rare, but 10% patients developed cytomegalovirus (CMV) reactivation. These patients rapidly responded to intravenous ganciclovir. One patient, allergic to cotrimoxazole prophylaxis, developed *Pneumocystis carinii* pneumonia. Alemtuzumab is highly effective as first-line treatment in patients with B-CLL. Prolonged treatment is important for maximal bone marrow response. Subcutaneous administration induced very few "first-dose" flulike symptoms and may reduce health care costs in comparison with the intravenous infusions. (Blood. 2002;100:768-773)

Introduction

Purine analogs and alkylating agents are still the cornerstones of treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). When used as first-line treatment, fludarabine induced an overall response (OR) of 63% including a complete remission (CR) rate of 20%.[1] Similar results have recently been reported with cladribine (2-CdA).[2] Chlorambucil induced fewer CRs but less severe side effects.[1,2] However, the disease is not yet curable and there is a great need for other treatment modalities with different mechanisms of action. Alemtuzumab (Campath-1H) is a humanized monoclonal antibody directed against CD52,[3] a nonmodulating glycosylated peptide antigen that is highly expressed on B-CLL cells (about 500 000 receptors/cell) and on normal lymphocytes[4] but not on hematopoietic ($CD34^+$) stem cells.[5] The effector mechanisms of alemtuzumab and other Campath antibodies are not fully understood but may include antibody-dependent cellular cytotoxicity,[3,6,7] complement-mediated cell lysis,[3,8] and induction of apoptosis.[9] Early pilot studies indicated that alemtuzumab could cause tumor regression in patients with advanced non-Hodgkin lymphoma (NHL).[10,11] However, subsequent phase II trials on patients with NHL indicated that the therapeutic effect was confined mainly to tumor cells in the blood and bone marrow, whereas bulky lymph nodes responded poorly.[12]

This led to pilot trials of alemtuzumab in B-CLL, because it is characterized by malignant lymphocytosis in blood and, in particular, infiltration of the bone marrow. Alemtuzumab has shown efficacy in trials of heavily pretreated patients with B-CLL where responses were achieved in 42% patients refractory to alkylating agents and in 33% of patients refractory to fludarabine therapy.[13,14]

In a pilot study, 9 patients with B-CLL received either subcutaneous or intravenous alemtuzumab as first-line treatment.[15] Long-lasting remissions without maintenance treatment were obtained in all but one patient and "first-dose" flulike symptoms were less pronounced in the patients who received subcutaneous injections. Similarly, fewer flulike symptoms were reported when small numbers of patients with refractory B-CLL were treated with subcutaneous alemtuzumab.[16]

The aim of this phase II study was to verify and extend these observations in a larger cohort of previously untreated, symptomatic patients with B-CLL, to assess the response rate, long-term efficacy, and toxicity of subcutaneous alemtuzumab as first-line

From the Departments of Hematology and Oncology, Karolinska Hospital, and Huddinge University Hospital, Stockholm, Sweden; and Therapeutic Antibody Center, Oxford, United Kingdom.

Submitted January 17, 2002; accepted March 18, 2002. Prepublished online as *Blood* First Edition Paper, June 7, 2002; DOI 10.1182/blood-2002-01-0159.

Supported by the Swedish Cancer Society, the Cancer Society in Stockholm, the King Gustaf V Jubilee Fund, the Arne and Sigbritt Lundberg Foundation, the Cancer and Allergy Foundation, Torsten and Ragnar Söderberg Foundation, the Gunnar Nilsson Cancer Foundation, and ILEX Oncology Inc. G.H. was supported by the Medical Research Council, the EP Abrahams Trust, and Millennium Pharmaceuticals Inc.

Reprints: Anders Österborg, Associate Professor, Department of Oncology, Karolinska Hospital, SE-171 76 Stockholm, Sweden; e-mail: anders.osterborg@ks.se.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

treatment, and to evaluate the clinical effects of prolonged (18 weeks) treatment.

Patients, materials, and methods

Study design

An open phase II trial was conducted at 4 clinics at the Karolinska Institute, (Stockholm, Sweden) in collaboration with the Therapeutic Antibody Centre (Oxford, United Kingdom). The primary objective was to assess the efficacy of alemtuzumab, administered subcutaneously with response rates (OR, CR, and partial remission [PR]) determined according to 1996 National Cancer Institute Working Group (NCIWG) criteria.[17] Secondary objectives were to assess the duration of remission and drug safety. The study was conducted with local ethics committee approval, and all patients gave written, informed consent prior to enrollment. Toxicity was graded according to criteria of the National Cancer Institute.

Patients

Adults, between 18 and 75 years of age, were eligible for inclusion in the study if they had a diagnosis of B-CLL, a World Health Organization performance status of 1 or less, a life expectancy of at least 12 weeks, were symptomatic,[17] required treatment,[17] and had not been treated previously. Serum creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase values had to be 125% or less of the upper limit of the normal range, unless attributable to the disease. Exclusion criteria were an active infection, pregnancy or lactation, human immunodeficiency virus–positive disease, autoimmune hemolysis or thrombocytopenia requiring treatment, or grade III or IV heart failure, according to the New York Heart Association functional classification.

Treatment

Alemtuzumab was obtained either from the Therapeutic Antibody Centre (patients no. 1-29) or from ILEX Oncology (San Antonio, TX; patients no. 30-41). The properties of the 2 alemtuzumab preparations are almost identical.[18] On day 1, 3 mg alemtuzumab was administered by subcutaneous injection in the thigh. If well tolerated, this dose was raised to 10 mg on day 3 and then raised to the target dose of 30 mg, split into 2 injection sites (1.5 mL at each site) on day 5. Dose escalation over a period of 1 to 2 weeks was used in the event of local skin erythema or edema. After the dose-escalation phase, and the disappearance of "first-dose" skin reactions, almost all patients self-administered alemtuzumab. The 30-mg dose was given 3 times weekly for a maximum of 18 weeks. If treatment was interrupted for more than 7 days, the dose was reinitiated at 3 or 10 mg. Treatment was stopped in the event of patients achieving a CR or fulfilling the criteria for progressive disease (PD).

Concomitant medications

Prophylactic medication against "first-dose" reactions included paracetamol (1 g orally) and antihistamines (clemastine 2 mg intravenously), given 30 minutes before the injections. Once all "first-dose" side effects had disappeared, clemastine and paracetamol prophylaxis was gradually withdrawn. Allopurinol (300 mg/d) was given for the first 4 weeks. Antiinfective prophylaxis, valacyclovir (500 mg tablets, twice daily), fluconazole (50 mg/d), and cotrimoxazole (twice daily, 3 times a week), was given during and for 8 weeks after completion of treatment.

Monitoring

At enrollment, a full physical examination was performed. This included assessment of lymph node, liver, and spleen size, a computed tomography (CT) scan of the thorax and abdomen, and full laboratory analysis of blood parameters. Bone marrow aspiration and trephine biopsy were performed and immunophenotyping of B-CLL cells in blood or bone marrow (CD19/CD5/CD23, CD19/CD5/CD52) was carried out by flow cytometry.

During treatment, blood counts and a differential were analyzed once weekly and serum electrolytes were measured and serum liver tests performed every 3 weeks. Physical examination, including tumor assessment, chest and abdominal CT scan (if initially abnormal), bone marrow aspiration, and trephine biopsy were carried out every 6 weeks. At completion of treatment all the above tests were repeated. Flow cytometry was performed to verify morphologic CR in the bone marrow.

During unmaintained follow-up, physical examination including assessment of lymph node, liver, and spleen size was performed each month between months 2 and 6 and quarterly thereafter. Blood counts were analyzed weekly for the first month, monthly during months 2 to 6, and quarterly thereafter. A chest and abdominal CT scan was performed twice yearly to a maximum of 2 years. Follow-up examinations were stopped if patients were diagnosed with PD. For patients in morphologic CR, bone marrow examination, including immunophenotyping, was repeated at 8 weeks after treatment and otherwise when clinically indicated.

End points

The primary efficacy end point used NCIWG-defined criteria.[17] CR was defined as freedom from clinical disease for at least 2 months with a "normal" blood count (hemoglobin $>$ 11g/dL, neutrophils $\geq 1.5 \times 10^9$/L, lymphocytes $\leq 4 \times 10^9$/L, platelets $> 100 \times 10^9$/L), no constitutional symptoms, no detectable lymphadenopathy, no hepatosplenomegaly, and less than 30% small lymphocytes in the bone marrow with no nodules. Nodular PR in the bone marrow was defined as less than 30% lymphocytes but with at least one detectable nodule. PR was defined by at least 50% reduction in the number of lymphocytes in the blood and at least 50% reduction in lymphadenopathy or hepatosplenomegaly (or both). At least one of the following had to be maintained for at least 2 months: hemoglobin above 11g/dL or 50% improvement, platelets more than 100×10^9/L, and neutrophils at least 1.5×10^9/L. PD was defined by lymphadenopathy, blood CLL lymphocyte count or hepatosplenomegaly increased by at least 50%, occurrence of newly affected lymph nodes, or histology showing a more aggressive picture.

Secondary end points were responses according to disease site, the time to achieve responses in blood, bone marrow, and lymph nodes, and the unmaintained time to treatment failure (time to fulfilling criteria for PD or requiring additional treatment for CLL).

Results

Forty-one patients, with a median age of 66 (range, 44-75 years), were enrolled. The majority of patients had advanced disease (Rai stage I, 10%; stage II, 21%; stage III, 54%; stage IV, 15%).[19] B symptoms (fever, night sweats, weight loss) were present in 63% of the patients (Table 1). The indication for treatment in the 4 patients with Rai stage I disease were B symptoms and additionally, 2 of

Table 1. Patient characteristics (n = 41)

Characteristic	Patients (%)
Age, y (median, range)	66 (44-75)
Mo since CLL diagnosis (median, range)	17 (1-273)
Rai stage, %	
I	10
II	21
III	54
IV	15
B symptoms, %	
Yes	63
No	37
Lymph node size, % (maximum diameter)	
No lymphadenopathy	17
5 cm or less	63
Greater than 5 cm	20

Table 2. Response (%) in 38 evaluable* B-CLL patients treated with subcutaneous alemtuzumab as first-line treatment

Group	OR	CR	PR	SD	PD
All patients, N = 38	87	19	68	8	5
Rai stage I or II, n = 11	100	9	91	0	0
Rai stage III or IV, n = 27	81	22	59	11	8
Age older than 65 y, n = 20	90	20	70	5	5
Age 65 years or younger, n = 18	83	17	66	11	6
Any lymph node greater than 5 cm in diameter, n = 7	86	0	86	14	0
All lymph nodes 5 cm or less in diameter, n = 24	88	21†	67	4	8
No lymphadenopathy, n = 7	86	29	57	14	0

SD indicates stable disease.
*Three patients who received only 1 week of treatment were excluded from the efficacy analysis.
†All CRs in this category were obtained in patients with lymph nodes < 2 cm in diameter.

these patients showed enlargement of the lymph nodes (> 6 cm), which required treatment.

Dosing

Three patients were withdrawn within the first week of the study due to local pain at injection site, fever, and fatigue, respectively. Among the remaining 38 patients, all of whom received at least 4 weeks of alemtuzumab treatment, 31% escalated to the final dose of 30 mg 3 times a week during the first week, 47% during week 2, and 11% during week 3. The remaining 4 patients required 4 to 7 weeks to reach the final thrice weekly dose of 30 mg/injection. The reasons for slower dose escalation were prolonged injection site reactions (3 patients) and fever (1 patient).

Twenty-five patients completed all 18 weeks of treatment. The main reasons for treatment withdrawal during weeks 4 to 17 were achievement of a CR at week 12 (2 patients), no response (NR; 1 patient at week 12), PD (2 patients both at week 12), infectious complications (3 patients at weeks 4, 11, and 11, respectively), hematologic toxicity (2 patients, both at week 12), generalized eczema (1 patient at week 8), and by mistake (2 patients at weeks 7 and 12, respectively).

The median cumulative dose of alemtuzumab administered to the patients was 1213 mg (range, 22-1793 mg).

Efficacy

The OR rate is shown in Table 2. Of the 38 patients who received more than 1 week of treatment, 7 achieved a CR (19%) and 26 achieved a PR (68%) giving an OR of 87% (95% CI, 76%-98%; 81% of intent-to-treat population). The OR in the 11 evaluable patients with Rai stage I or II disease was 100% compared to 81% in the 27 patients with Rai stage III or IV disease. The OR was 90% in patients older than 65 years and 83% in patients 65 years old or younger (Table 2). The OR in 7 patients with large lymph nodes (at least one lymph node > 5 cm in diameter) was 86%. None of the patients with large lymph nodes achieved a CR. The OR in 24 patients with small or moderate lymph nodes (all nodes ≤ 5 cm) was 88%, and in patients with no lymphadenopathy it was 86%. There was no difference in OR rate between the 2 alemtuzumab preparations used in the study.

Responses in relation to disease site are shown in Table 3. CLL cells were cleared from the blood in all but 2 patients after a median time of 21 days (range, 7-63 days). The OR in the bone marrow was 79%. In 45% of patients a morphologic CR was seen and verified by negative 3-color flow cytometry, and additionally, 21% patients showed a nodular PR. Lymph nodes responded in 87% patients, 58% of which were PR. A CR with regard to lymphadenopathy was achieved in 29% patients, all of whom had small (< 2 cm in diameter) lymph nodes.

The cumulative response rate at various tumor sites in relation to length of treatment in patients responding to alemtuzumab treatment are shown in Table 4. In 10% of the patients, maximum tumor cell reduction in the bone marrow was achieved after 6 weeks of treatment, but in more than 50% of the patients the best bone marrow response was achieved after 18 weeks of treatment. This is in contrast to the lymph nodes, in which 42% patients achieved maximum tumor reduction after 6 weeks of treatment. The median time to treatment failure has not yet been reached, (18+ months; range, 7-44+ months).

Safety

"First-dose" reactions. Nonhematologic "first-dose" side effects are shown in Table 5. Local injection site reactions were seen in 37 of 41 (90%) patients. Grade I reactions (erythema/edema) were seen in 11 (27%) patients and grade II reactions (including pruritus and slight pain) in 25 (61%) patients. One patient experienced grade III local pain, leading to discontinuation of alemtuzumab after 1 week of treatment. The erythema was up to 30 cm in diameter in some patients. These reactions disappeared during continued treatment, usually within 2 weeks. Two patients with prolonged erythema/edema were switched to intravenous treatment. One of these returned to subcutaneous administration at a later date without a recurrence of the local reaction at the injection site.

Table 3. Response (%) in relation to disease site

Site	OR	CR	Nodular PR	PR
Blood, n = 38	97	95	—	2
Bone marrow, n = 38	79	45*	21	13
Lymph nodes, n = 31	87	29	—	58
Spleen, n = 28	90	36	—	54

*Verified by negative 3-color flow cytometry.

Table 4. Cumulative OR rate (%) in relation to treatment duration and tumor site in B-CLL patients who responded to alemtuzumab therapy

	Proportion (%) of responding patients		
Tumor site	Wk 6	Wk 12	Wk 18
Blood, n = 37	100*	100	100
Bone marrow, n = 30	10	45	100
Lymph nodes, n = 27	42	69	100
Spleen, n = 25	29	54	100

*Median time to CR in blood was 21 days (range, 7-63 days).

Table 5. "First-dose" reactions* following subcutaneous administration of alemtuzumab as first-line treatment in 41 patients with B-CLL

Event	NCI Grade I/II, %	NCI Grade III†, %
Fever	68	2‡
Rigor	15	2
Rash/urticaria	0	0
Hypotension	0	0
Dyspnea	0	0
Nausea/vomiting	0	0
Diarrhea	0	0
Headache	0	0
Fatigue	5	2‡
Local injection site reaction	88	2‡

*Most side effects disappeared after 1 to 2 weeks during continued alemtuzumab treatment.

†No grade IV reactions occurred.

‡Three patients were withdrawn from the study after 1 week due to grade III fever, fatigue, and pain at injection site, respectively.

Most other "first-dose" reactions, which are frequently seen after intravenous administration of alemtuzumab,[12-14] were rare or absent in this study. Transient rigor was seen in 17% patients, but there were no episodes of rash/urticaria, bronchospasm, hypotension, or nausea. Fatigue was observed in 3 patients, one of which was grade III and resulted in withdrawal of the patient from the study after 1 week of treatment. Grade I to II fever was observed in 68% of patients but disappeared rapidly during continued treatment. One patient who repeatedly reacted with grade III fever (even after 1.5 mg alemtuzumab) was withdrawn from the study after 1 week.

After the first 2 to 3 weeks, almost all side effects had disappeared and patients had started to self-administer alemtuzumab at home. There was no difference in the incidence or severity of "first-dose" reactions between the 2 alemtuzumab preparations used in the study.

Other side effects. Following cessation of the "first-dose" side effects, alemtuzumab was well tolerated in most patients. One patient developed generalized eczema and alemtuzumab was withdrawn after 8 weeks of treatment. Another patient developed autoimmune thyroiditis (without Graves disease), which required thyroxin substitution. Transformation to a high-grade lymphoma was observed in 2 patients.

Hematologic toxicity. Hematologic toxicity is shown in Table 6. Apart from long-lasting lymphocytopenia, which occurred in all patients, 21% of patients developed transient grade IV neutropenia after a median time of 4 weeks (range, 1-8 weeks). Alemtuzumab treatment was temporarily stopped in 7 patients, until their neutrophil counts had increased to more than 0.9×10^9/L. Five (13%) patients had 2 or more episodes of transient grade IV neutropenia. These patients received granulocyte colony-stimulating factor (G-CSF) and a few injections were usually enough to raise their granulocyte counts sufficiently. None of the patients developed febrile neutropenia. One patient who developed prolonged neutropenia but did not receive G-CSF was withdrawn from the study at week 12. Another patient developed an episode of autoimmune thrombocytopenia, which led to withdrawal from the study after 12 weeks.

Infectious complications. Alemtuzumab was generally well tolerated, with no episodes of febrile neutropenia or major (> grade I) bacterial infections. Reactivation of cytomegalovirus (CMV), verified by polymerase chain reaction, caused fever without pneumonitis in 4 patients after 4, 5, 11, and 12 weeks of treatment, respectively. Three patients received intravenous ganciclovir treatment and responded promptly. One patient recovered spontaneously. In 2 of these 4 cases, alemtuzumab treatment was restarted afterward while the patient received oral ganciclovir prophylaxis without further CMV problems.

One patient developed *Pneumocystis carinii* pneumonia (PCP) after 11 weeks of treatment. This patient was allergic to cotrimoxazole and was the only patient who did not receive any PCP prophylaxis.

No late-occurring infectious complications or other side effects were observed in any of the patients during long-term unmaintained follow-up.

Discussion

This study demonstrates an OR rate of more than 80% for subcutaneous alemtuzumab in previously untreated, symptomatic patients with B-CLL. Long-lasting, unmaintained remissions were obtained in most patients. These responses appear to be as high as those obtained with purine analogs such as fludarabine and cladribine when used as first-line treatment.[1,2,20] Furthermore, the responses observed with alemtuzumab treatment seem to compare favorably with those obtained with rituximab therapy at standard doses in symptomatic patients with B-CLL.[21,22]

A CR in the blood was achieved in all but 2 patients after a median time of 21 days. This is similar to intravenous administration of alemtuzumab.[13] At the beginning of this study, the biodistribution and pharmacokinetics of alemtuzumab whether given intravenously or subcutaneously were not known. The chosen sample times for measurement of drug levels using a validated indirect immunofluorescence assay[23] did not give sufficient information for proper calculation of the pharmacokinetic parameters. Blood levels above 1 μg/mL could be detected in nearly all patients during the therapy, although in some cases they did not reach this level till about 10 weeks (G.H. et al, unpublished observation, December 2001). The peak trough levels varied quite widely between patients, and this may be associated with the tumor burden. Two patients who received alemtuzumab intravenously for the majority of their course did not achieve any higher blood levels than in others; in fact, both were actually lower than the mean. These preliminary results, as well as the high OR rate obtained in the present study indicate an adequate bioavailability when alemtuzumab is administered subcutaneously.

The response rate was almost as high in patients with Rai stage III or IV as in those who had stage I or II disease. This may be because alemtuzumab is particularly effective in eradicating malignant cells in the bone marrow, thereby improving or normalizing peripheral blood counts. This finding has been repeatedly observed in previous trials on advanced CLL and NHL.[12-14] Preferential clearance of tumor cells from blood and bone marrow was also observed in the present trial in which more than 60% of the patients achieved a CR or close to CR in the bone marrow. Most

Table 6. Hematologic toxicity (%) during subcutaneous first-line treatment with alemtuzumab in 38 patients with B-CLL who received more than 1 week of therapy

	NCI grading		
	0-I	II-III	IV
Anemia	61	39	0
Neutropenia	26	53	21*
Thrombocytopenia	84	11	5

*Occurred after a median time of 4 weeks (range, 1-8 weeks).

importantly, the response rate was equally high in patients older than 65 years and a high response rate was still seen in the 10 patients older than 70 years, 9 of whom responded to alemtuzumab. This may reflect the good tolerability of subcutaneous alemtuzumab observed in the present study.

In contrast to previous trials on patients with advanced CLL and NHL,[12,14,15] the effect on enlarged lymph nodes appears to be more pronounced when alemtuzumab is used as first-line treatment. The reason for this difference is not known. Even patients with large lymph nodes (> 5 cm) responded, but CRs were only observed in patients with small (< 2 cm) lymph nodes. In most patients, there was no further reduction of the lymph node size after 6 to 12 weeks of treatment. This is in contrast to the bone marrow, where more than half of the patients required 18 weeks of treatment to reach the maximum tumor cell reduction. Long-term alemtuzumab treatment may therefore be of major importance to achieve high-quality remissions in the bone marrow.

This study did not include a second response evaluation 3 months after the end of treatment. Due to the emerging data on late responses in patients with NHL following rituximab treatment,[24] the last few patients in our study were assessed 2 to 3 months after the end of treatment. Further tumor regression was observed in some of the patients (data not shown).

The treatment was generally well tolerated and almost all patients could, after dose escalation, self-administer alemtuzumab. Acute administration-related events such as rigor, rash or urticaria, nausea, hypotension, and bronchospasm appeared to be rare or absent. This is in sharp contrast to what has been reported following intravenous infusion of alemtuzumab.[12,14,15,25,26] The reason for the diminished toxicity observed with subcutaneous administration is not clear. It appears that subcutaneous administration induced a local inflammatory reaction at the injection site rather than general, cytokine-release mediated "flulike" symptoms. Whether it may also be explained by a different pharmacokinetic profile, such as lower peak level than with intravenous infusion, is not yet known.

During the first week of treatment, the majority of patients developed transient grade I or II injection site skin reactions that required an individual dose escalation that was slower, compared to intravenous administration.[14] The areas of erythema and edema were sometimes quite large. In some patients, corticosteroids were given intravenously without any apparent effect on the intensity or the duration of the skin reactions. Preliminary data indicate that prophylactic use of corticosteroids may reduce the "first-dose" flulike symptoms, particularly rigor, following intravenous administration of alemtuzumab[26] (and our unpublished observations). Thus, given that the injection site skin reactions observed during week 1 to 2 of this trial may be quite large, requiring individual dose escalation of alemtuzumab, it might be that intravenous administration of alemtuzumab (with concomitant corticosteroid prophylaxis) may be used in the future, during week 1 to 2, followed by a switch to subcutaneous administration for the remaining treatment period, for maximum patient convenience and reduced health care costs. The feasibility and side effects of such a therapeutic strategy will be addressed in a prospective clinical trial.

About one fifth of the patients in this study developed transient grade IV neutropenia (without febrile episodes), a finding similar to those in patients with advanced CLL.[13] The mechanism of alemtuzumab-induced neutropenia is still unknown. Some patients had prolonged or recurrent episodes of neutropenia that justified the use of G-CSF to not further delay treatment.

Infectious complications were fewer than in previous studies on advanced CLL and NHL. However, CMV reactivation caused fever without pneumonitis in 4 (10%) patients. None of these CMV infections were considered dangerous. One patient recovered spontaneously and the other 3 responded promptly to intravenous ganciclovir. CMV reactivation has been reported to occur typically after 4 to 8 weeks of treatment,[26,27] but 2 patients in the present study were diagnosed with CMV after 11 and 12 weeks of treatment, respectively. CMV reactivation may be one of the most common infectious complications during alemtuzumab treatment and may have been underreported in previous trials. CMV must always be excluded in the event of fever of unknown origin while the patient is on alemtuzumab therapy. One patient in the present study developed PCP. This was the only patient in the trial who was not on prophylaxis because she was allergic to cotrimoxazole. Pentamidine inhalations are therefore strongly recommended in these instances.

In summary, this study indicates that alemtuzumab is a highly active agent in previously untreated patients with CLL. Prolonged treatment appears to be of major importance in the achievement of high-quality remissions in the bone marrow. The side effects reported in this trial indicate that alemtuzumab has an acceptable safety profile when used as first-line treatment in CLL, provided that antibiotic prophylaxis is used and the patients are closely observed, especially concerning the risk of CMV reactivation. The subcutaneous route of administration may confer major advantages once the injection site skin reactions have subsided, both in terms of practical aspects for the patients (self-administration is feasible) and in reducing costs for the health care system.

Acknowledgments

We thank the team at the Therapeutic Antibody Centre who produced much of the antibody used in this study. The excellent secretarial help of Ms Gerd Ståhlberg is highly appreciated.

References

1. Rai KR, Peterson BS, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med. 2000;343:1750-1757.
2. Robak T, Blonski J, Kasznicki M, et al. Cladribine with prednisone versus chlorambucil with prednisone as first-line therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial. Blood. 2000;96:2723-2729.
3. Riechmann L, Clark M, Waldmann H, Winter G. Reshaping human antibodies for therapy. Nature. 1988;332:323-327.
4. Rossmann ED, Lundin J, Lenkei R, Mellstedt H, Osterborg A. Variability in B-cell antigen expression: implications for the treatment of B-cell lymphomas and leukemias with monoclonal antibodies. Hematol J. 2001;2:300-306.
5. Gilleece MH, Dexter TM. Effect of Campath-1H antibody on human hematopoietic progenitors in vitro. Blood. 1993;82:807-812.
6. Dyer MJ, Hale G, Hayhoe FG, Waldmann H. Effects of CAMPATH-1 antibodies in vivo in patients with lymphoid malignancies: influence of antibody isotype. Blood. 1989;73:1431-1439.
7. Greenwood J, Clark M, Waldmann H. Structural motifs involved in human IgG antibody effector functions. Eur J Immunol. 1993;23:1098-1104.
8. Heit W, Bunjes D, Wiesneth M, et al. Ex vivo T-cell depletion with the monoclonal antibody Campath-1 plus human complement effectively prevents acute graft-versus-host disease in allogeneic bone marrow transplantation. Br J Haematol. 1986;64:479-486.
9. Rowan W, Tite J, Topley P, Brett SJ. Cross-linking of the CAMPATH-1 antigen (CD52) mediates growth inhibition in human B- and T-lymphoma cell lines, and subsequent emergence of CD52-deficient cells. Immunology. 1998;95:427-436.
10. Hale G, Dyer MJ, Clark MR, et al. Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1H. Lancet. 1988;2:1394-1399.
11. Lim SH, Davey G, Marcus R. Differential response in a patient treated with Campath-1H

monoclonal antibody for refractory non-Hodgkin lymphoma. Lancet. 1993;341:432-433.

12. Lundin J, Osterborg A, Brittinger G, et al. CAMPATH-1H monoclonal antibody in therapy for previously treated low-grade non-Hodgkin's lymphomas: a phase II multicenter study. European Study Group of CAMPATH-1H Treatment in Low-Grade Non-Hodgkin's Lymphoma. J Clin Oncol. 1998;16:3257-3263.
13. Osterborg A, Dyer MJ, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. J Clin Oncol. 1997;15:1567-1574.
14. Keating MJ, Byrd JC, Rai K, et al. Multicenter study of Campath-1H in patients with chronic lymphocytic leukemia (B-CLL) refractory to fludarabine [abstract]. Blood. 1999;94:3118.
15. Osterborg A, Fassas AS, Anagnostopoulos A, Dyer MJ, Catovsky D, Mellstedt H. Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia. Br J Haematol. 1996;93:151-153.
16. Bowen AL, Zomas A, Emmett E, Matutes E, Dyer MJ, Catovsky D. Subcutaneous CAMPATH-1H in fludarabine-resistant/relapsed chronic lymphocytic and B-prolymphocytic leukaemia. Br J Haematol. 1997;96:617-619.
17. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood. 1996;87:4990-4997.
18. Phillips J, Drumm A, Harrison P, et al. Manufacture and quality control of CAMPATH-1 antibodies for clinical trials. Cytotherapy. 2001;3:233-242.
19. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46:219-234.
20. Johnson S, Smith AG, Loffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet. 1996;347:1432-1438.
21. Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. Blood. 2001;98:1326-1331.
22. Hainswirth JD, Litchy S, Burris HA, Greco FA. Rituximab as first-line and maintenance therapy for patients with small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL). Blood. 2001;98:363a.
23. Rebello P, Hale G. Pharmacokinetics of CAMPATH-1H: assay development and validation. J Immunol Methods. 2002;260:285-302.
24. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825-2833.
25. Pangalis GA, Dimopoulou MN, Agelopoulou MK, et al. Campath-1H in B-chronic lymphocytic leukemia: report on a patient treated thrice in a 3-year period. Med Oncol. 2000;17:70-73.
26. Hagberg H, Lundin J, Repp R, et al. Phase II study of alemtuzumab in patients with advanced mycosis fungoides/Sezary syndrome. Blood. 2001;98:806a.
27. Kennedy B, Rawstron A, Richards S, Hillmen P. Campath-1H in CLL: immune reconstitution and viral infections during and after therapy. Blood. 2000;96:707.