ORIGINAL ARTICLE

Low-dose subcutaneous alemtuzumab in refractory chronic lymphocytic leukaemia (CLL): results of a prospective, single-arm multicentre study

A Cortelezzi[1,2], MC Pasquini[2], A Gardellini[2], U Gianelli[3], A Bossi[4], G Reda[2], B Sarina[5], P Musto[6], W Barcellini[7], A Neri[1,2] and GL Deliliers[1,2]

[1]Department of Medical Sciences, University of Milan, Milan, Italy; [2]Hematology 1—Bone Marrow Transplantation Unit, IRCCS Foundation 'Policlinico Mangiagalli and Regina Elena', Milan, Italy; [3]Department of Pathology, University of Milan and San Paolo Hospital, Milan, Italy; [4]Department of Medical Statistics, University of Milan, Milan, Italy; [5]Oncology/Hematology Department, Bone Marrow Unit, Istituto Clinico Humanitas, Rozzano, Italy; [6]Unit of Hematology and Stem Cell Transplantation, IRCCS-CROB, Oncology Referral Center of Basilicata, Rionero in Vulture, Potenza, Italy and [7]Hematology 2 Unit, IRCCS Foundation 'Policlinico Mangiagalli and Regina Elena', Milan, Italy

Alemtuzumab is active in chronic lymphocytic leukaemia (CLL) patients refractory to alkylators and fludarabine. The aim of this study was to determine the efficacy and safety of subcutaneous alemtuzumab at low dose (10 mg three times per week, for 18 weeks) to 49 patients with pre-treated CLL. The overall response rate was 53%, including 27% of complete responses; it was 42% in patients over 70 years, and 54% in the fludarabine-resistant patients. Forty-five percent of the patients with an unfavourable karyotype responded, including 60% of those with the 17p- aberration. After a median follow-up of 25 months, the median overall time to disease progression was 8 months (responders 12 months, non-responders 4 months). The median overall time to alternative treatment was 9 months (responders 17 months, non-responders 6 months) and median overall survival was 30 months. The treatment was well tolerated: grade IV neutropenia was observed in 17%, and cytomegalovirus (CMV) reactivation in 24% of the patients, with no CMV disease. We observed a total of 30 infections (50% during treatment and 50% during the 12-month follow-up), only one-third of which was severe. This study confirms that low-dose subcutaneous alemtuzumab is effective in poor prognosis CLL, and has a particularly favourable toxicity profile.

Introduction

Chronic lymphocytic leukaemia (CLL) patients who are refractory to front-line therapy (primarily or after an initial response) have a poor prognosis. This is particularly true of those who are resistant to fludarabine-containing regimens, whose life expectancy is no more than 1 year regardless of therapeutic regimen.[1]

When treating patients with refractory CLL, great care has to be paid to the variables that are useful in predicting therapeutic response. Deletion 17p is very important because it has been associated with little or no response to alkylators and fludarabine, and with a blunted response to more complex and efficacious fludarabine-containing regimens such as the combination of fludarabine, cyclophosphamide and rituximab.

It is also known that new genomic aberrations (notably 17p-) can be acquired during the course of the disease, which means their incidence is greater in advanced CLL.[2,3]

Alemtuzumab is a humanised chimeric monoclonal antibody (MoAb) that targets the CD52 antigen.[4] It been found to be effective in CLL when used alone as both front-line and salvage therapy,[5] and also seems to be effective in patients whose leukaemic cells carry the 17p deletion.[6,7] However, although the first published studies of alemtuzumab in the treatment of CLL go back more than 10 years,[8] some areas of uncertainty still remain. These mainly concern the fear of adverse events related to the profound lymphopenia and associated infections induced by the drug when the classic and consolidated intravenous schedule of 30 mg three times a week for 12 weeks is used because, although highly effective, it may lead to infusion-related side effects and potentially life-threatening infections.[1] This is crucial when dealing with very old CLL patients (still the majority of those who undergo treatment) and those already severely immunocompromised by advanced disease and earlier therapies. It has been shown that the subcutaneous administration of alemtuzumab for a longer period is highly effective as first-line treatment, giving rise to fewer and less severe systemic symptoms and thus leading to greater patient compliance.[6,9] Favourable results have also been obtained using much lower cumulative and per dose amounts of the drug, particularly in the setting of maintenance/consolidation therapy.[10]

The aim of this article is to update our earlier findings in a smaller cohort of patients[9] concerning the safety and efficacy of subcutaneous low-dose alemtuzumab treatment in patients with refractory CLL. In describing the results of this less aggressive approach to advanced CLL with alemtuzumab monotherapy, this paper will concentrate particularly on patients with adverse prognostic features such as the 17p deletion, an advanced clinical stage, advanced age and fludarabine resistance.

Materials and methods

The primary objective of this prospective, multicentre, single-arm phase II study, which involved four Italian Haematology Units, was to verify the efficacy of low-dose alemtuzumab, which was evaluated on the basis of the response rate, assessed on the basis of the 1996 National Cancer Institute (NCI) Working Group criteria,[11] time to disease progression (TTP) and time to alternative treatment (TTT) in the intention-to-treat population.

The secondary objectives were to assess overall survival (OS) in the intention-to-treat population and verify the safety of the drug, which was carried out by carefully documenting any grade III–IV serious adverse events: that is any local and systemic first dose reactions, or infectious complications occurring during alemtuzumab therapy or in the 6 months after its discontinuation. The study was approved by the local Ethics Committee, and all of the patients gave their written informed consent before enrolment, which took place between September 2003 and June 2007; the follow-up period finished in April 2008.

Patients

Adults aged more than 18 years were considered eligible for study entry if they had a diagnosis of CLL (as defined by the 1996 NCI criteria),[11] a WHO performance status of $\leqslant 2$ and a life expectancy of at least 3 months, were symptomatic and required treatment, and if they had failed to respond to earlier treatment with an alkylating agent or fludarabine. Alkylator or fludarabine failure was defined as a failure to achieve partial or complete remission (PR or CR) on at least one alkylator- or fludarabine-containing regimen; disease progression while receiving alkylator or fludarabine treatment; or (in the case of responders) diseases progression within 6 months of the last dose. The additional inclusion criteria were bilirubin, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase levels less than three times the upper normal limit, and serum creatinine levels less than twice the upper normal range, unless the values were attributable to the disease.

The exclusion criteria were pregnancy or lactation, human immunodeficiency virus-positive disease, active infection, or grade IV heart failure according to the New York Heart Association functional classification.[12]

Treatment schedule

Alemtuzumab 3 mg was subcutaneously administered on day 1; if this dose was well tolerated, it was increased to the target dose of 10 mg on day 3, which was subsequently given three times weekly for a maximum of 18 weeks and a maximum cumulative dose of 544 mg. The treatment was discontinued permanently in the case of progressive disease (PD), life-threatening infections, grade IV haematological and/or non-haematological complications or the withdrawal of patient consent; it was temporarily interrupted if peripheral blood neutrophil counts fell to $<1.0 \times 10^9/l$ despite supportive granulocyte colony-stimulating factor (G-CSF) therapy or platelet counts to $< 20 \times 10^9/l$, or in the case of grade $>$II complications.

First dose reaction prophylaxis included acetaminophen (1 g p.o.) and antihistamines (chlorpheniramine 10 mg e.v.) given 30 min before the injections; to minimise local reactions, hydrocortisone 5 mg was directly added to the alemtuzumab solution inside the syringe. This medication was restricted to the first 1–2 weeks depending on patient symptoms, and then gradually withdrawn. Anti-infective prophylaxis with oral cotrimoxazole (one tablet b.i.d. three times a week) and acyclovir (400 mg t.i.d.) was given during treatment and for at least 2 months afterwards. The patients were monitored weekly for cytomegalovirus (CMV) reactivation by means of early pp65 antigenemia tests until January 2006, when the tests were replaced by CMV DNA quantification.

On enrolment, the patients underwent a physical examination, computed tomography of the thorax and abdomen, and extensive laboratory analyses of blood parameters. Bone marrow aspiration and a trephine biopsy were performed, and

blood or bone marrow B-CLL cells (CD19/CD5/CD23, CD38, sIg, ZAP70) were immunophenotyped by means of flow cytometry or immunoistochemistry. During treatment, they underwent weekly physical examinations, blood counts with differential, and serum electrolyte, liver and renal tests and, at the end of treatment, a physical examination, including tumour assessment, chest and abdominal computed tomography (if initially abnormal), bone marrow aspiration and a trephine biopsy. Two-colour flow cytometry was used to verify morphological CR in bone marrow.

During the follow-up, the patients underwent physical examinations and blood counts every month between months 2 and 6, and every 3 months thereafter. Their bone marrow was examined every 6 months after the completion of immunotherapy until signs of a relapse were observed.

Demographic and baseline clinical characteristics

Forty-nine patients (33 males and 16 females) were enrolled and received alemtuzumab subcutaneously according to our protocol, all of who were evaluable for response (on an intention-to-treat basis) and toxicity. Table 1 shows their baseline characteristics. Their median age was 68 years (range 40–83): 19 patients (39%) were older than 70 years. Forty-six patients (94%) were in Binet's stage B or C.

Table 1 Patient demographics (*n* 49)

Males, *n* (%)	33 (67)
Females, *n* (%)	16 (33)
Median age, years (range)	68 (40–83)
<70 years, *n* (%)	30 (61)
⩾70 years, *n* (%)	19 (39)
Time since diagnosis of CLL, years (range)	62.5 (7–215)
Binet stage at study enrolment, n (%)	
A	3 (6)
B	26 (53)
C	20 (41)
Unfavourable cytogenetics	31 (63)
17p-	10 (20)
Normal karyotype and isolated 13q-, *n* (%)	18 (37)
ZAP70+, *n* (%)	30 (68)
CD38+, *n* (%)	22 (54)
Median number of prior different regimens (range)	2 (1–5)
Type of prior therapies, n (%)	
Alkylating agents	49 (100)
Fludarabine-containing regimens	26 (53)
Rituximab-containing regimens	14 (29)
Earlier infections, n (%)	29 (59)
Chronic HBV infection	3 (6)
Occult HBV infection	5 (10)
HCV	4 (8.1)
VZV	6 (12)
CMV	1 (2)
Cutaneous TBC	1 (2)
Pseudomonas aeruginosa pneumonia	1 (2)
Pseudomonas aeruginosa otitis	1 (2)
Pneumonia of unknown origin	7 (14)
Earlier haemolytic anaemia (AIHA), *n* (%)	7 (14)
Earlier idiopatic thrombocytopenic purpura (ITP), *n* (%)	1 (2)

AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; TBC, tuberculosis; VZV, varicella zoster virus.

Thirty-one patients (63%) showed an unfavourable cyto-genetic profile, including 17p deletion (10 patients, 23%), 11q deletion, trisomy 12, 6q deletion and complex abnormalities; 18 patients (37%) had a normal karyotype or isolated 13q deletion. Fifty-four percent showed high CD38 expression, and 68% were ZAP-70 positive.

The patients had received a median of two earlier lines of therapy (range 1–5). All of them were refractory to alkylating agents: 26 (53%) were also resistant to fludarabine-containing regimens, and one-third to rituximab-containing regimens.

Twenty-nine patients (59%) had experienced at least one infectious episode in the 6 months preceding alemtuzumab therapy. Three patients presented chronic hepatitis B surface antigen (HBsAg) + HBV (hepatitis B virus) infection, and a further five had occult HBV infection. Seven patients (14%) were diagnosed as having autoimmune haemolytic anaemia (AIHA) during the 6 months preceding alemtuzumab therapy, and one suffered an episode of idiopathic thrombocytopenic purpura (ITP).

All of the patients received alemtuzumab for at least 4 weeks (median 16 weeks; range 4–18), for a median cumulative dose of 480 mg (range 120–544). Twenty-seven patients completed the planned treatment, and 22 discontinued the treatment prematurely because of CR (11/49, 37%), documented PD (5/49, 10.2%), the development of autoimmune complications (ITP and AIHA, one patient each), grade IV infections (two patients) or a second tumour (two patients). The treatment was temporarily interrupted in 12 patients because of transient CMV reactivation.

Statistical analysis

The overall response (OR = CR + PR) and CR rates were estimated with their 95% confidence intervals (CIs). Overall survival and the TTP were calculated from the start of alemtuzumab treatment to the date of death or relapse; the TTT was calculated from the start of alemtuzumab treatment to the date of the change in treatment. Kaplan–Meier survival curves (OS, TTP and TTT) were drawn up for the responders (CR + PR), non-responders (stable disease (SD) + PD) and risk factor groups (cytogenetics, age, stage, CD38/ZAP70 expression, and fludarabine and rituximab resistance), and median survival was estimated with its approximate 95% CI. The differences between the populations in the probability of death, relapse or new treatment at any time point were tested using the log-rank test. P values of less than 0.05 were considered significant. The data were processed and statistically analysed using version 9.1 SAS software (SAS Institute, Cary, NC, USA).

Results

Response

The OR rate according to the 1996 NCI-WG criteria was 53% (95% CI 38–67%), and included 27% of CRs (95% CI 15–41%) (Table 2); 10% of the patients experienced PD during the treatment, and approximately one-third had SD at the end of therapy. The OR rate was 42% in the patients older than 70 years.

Forty-five percent of the patients with an unfavourable karyotype responded to alemtuzumab, compared with 69% of those with a normal karyotype or isolated 13q deletion. The OR rate was 60% (including 20% of CRs) in the patients with the 17p- aberration. Favourable responses were documented in 46% of the patients with CD38-positive leukaemic cells and 47% of those with ZAP70-positive cells.

When low-dose alemtuzumab was given as second-line therapy (to 18 patients treated earlier with chlorambucil alone), the OR rate was 50% and the CR rate as high as 33%. The fludarabine-resistant patients showed the same OR rate as the overall population (54%), with a slightly lower percentage of CRs (23%); the patients who were resistant to both rituximab

Table 2 Responses by clinical and biological characteristics

Characteristic	OR	CR	PR	SD	PD
Global response, n (%)	26 (53.1)	13 (26.5)	13 (26.5)	18 (36.7)	5 (10.2)
Peripheral blood, n (%)	38 (77.6)	31 (63.3)	7 (14.3)	10 (20.4)	1 (2.0)
Bone marrow, n (%)	26 (63.4)	23 (56.1)	3 (7.3)	15 (36.6)	—
Lymph nodes, n (%)	26 (53.1)	16 (32.7)	10 (20.4)	18 (36.7)	5 (10.2)
Spleen, n (%)	14 (51.9)	12 (44.4)	2 (7.4)	11 (40.7)	2 (7.4)
Gender, n (%)					
Male	15 (45.5)	7 (21.2)	8 (24.2)	13 (39.4)	5 (15.2)
Female	11 (68.8)	6 (37.5)	5 (31.3)	5 (31.3)	0
Unfavourable cytogenetics, n (%)	14 (43.7)	5 (15.6)	9 (28.1)	14 (43.7)	3 (9.3)
17p-, n (%)	6 (60.0)	2 (20.0)	4 (40.0)	4 (40.0)	0
Age, n (%)					
<70 years	18 (60.0)	8 (26.7)	10 (33.3)	10 (33.3)	2 (6.7)
⩾70 years	8 (42.1)	5 (26.3)	3 (15.8)	8 (42.1)	3 (15.8)
Binet stage, n (%)					
A	3 (100)	3 (100)	0	0	0
B	13 (50)	6 (23.1)	7 (26.9)	10 (38.5)	3 (11.5)
C	10 (50)	4 (20)	6 (30)	8 (40)	2 (10)
ZAP 70+, n (%)	14 (46.7)	6 (20.0)	8 (26.7)	13 (43.3)	3 (10.0)
CD38+, n (%)	10 (45.5)	5 (22.7)	5 (22.7)	9 (40.9)	3 (13.6)
Failed on fludarabine, n (%)	14 (53.8)	6 (23.1)	8 (30.8)	9 (34.6)	3 (11.5)
Failed on rituximab, n (%)	6 (42.9)	3 (21.4)	3 (21.4)	6 (42.9)	2 (14.3)

CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

and fludarabine showed an OR rate of 43%, including 21% of CRs. The CR rate in the 20 stage C patients was lower (20%), although the OR rate (50%) was comparable with that in the overall population.

None of the differences in the OR or CR rates between the considered patient subgroups based on gender, age, clinical stage, karyotype, CD38 or ZAP70 expression, or fludarabine or rituximab resistance was statistically significant. VHIg mutational status was assessed in fewer than half of the patients, and so no conclusion can be drawn concerning its impact on the response to alemtuzumab therapy.

In terms of sites of leukaemic involvement, a response was obtained in peripheral blood in 78% of the cases, in bone marrow in 63% and in lymph nodes and spleen in 50%. The median time to a 1-log depletion of peripheral blood lymphocytes was 4 weeks (range 1–16). In relation to the kinetics of response in blood and lymph nodes, the median time to the maximum tumour reduction was 5.5 weeks for blood, 6 weeks for lymph nodes, 9 weeks for spleen and 15 weeks for bone marrow.

Overall survival
After a median follow-up of 25 months (range 2–56), 27 patients had died (55%), including 11/26 responders (42%) and 16/23 non-responders (70%) (Figure 1). The 12-month probability of survival was 0.96 ± 0.04 s.e. in responders and 0.65 ± 0.10 s.e. in non-responders, and the 24-month probability was, respectively, 0.77 ± 0.09 s.e. and 0.52 ± 0.11. Median OS was 30 months (95% CI 25–40 months) with a significant difference ($P = 0.047$) between responders and non-responders (Figure 1). Five CR patients died: two in CR and three after PD. The presence of an unfavourable cytogenetical profile did not have an impact on survival, nor did an age of more than 70 years, the presence of p53 deletion or the expression of CD38 or ZAP70.

Time to disease progression
Thirty-eight patients (78%) progressed during the observation period, including 22/23 non-responders (96%) and 16/26 responders (62%) (Table 3). The median overall TTP was 8 months (95% CI 5–11 months), with a significant difference ($P = 0.0004$) between the responders (12 months, 95% CI 10–15 months) and non-responders (4 months, 95% CI 4–6 months) (Figure 1).

Time to alternative treatment
Thirty-three patients (67%) received alternative treatment, including 42% of the responders. The median overall TTT was 9 months (95% CI 6–12 months), with a significant difference ($P < 0.0001$) between responders (17 months, 95% CI 12–26 months) and non-responders (6 months, 95% CI 4–6 months) (Figure 1).

Safety and tolerability
The alemtuzumab regimen was generally well tolerated, and most of the observed adverse events were minor and transient. (Table 4) Approximately two-thirds of the patients experienced peripheral blood cytopenia, but this was WHO grades III–IV in fewer than 5% of the anaemic patients, one-sixth of the thrombocytopenic patients and roughly one-third of the neutropenic patients. Alemtuzumab treatment had to be interrupted for a median of 2 weeks (range 1–3 weeks) in nine of the patients with an absolute neutrophil count of less than
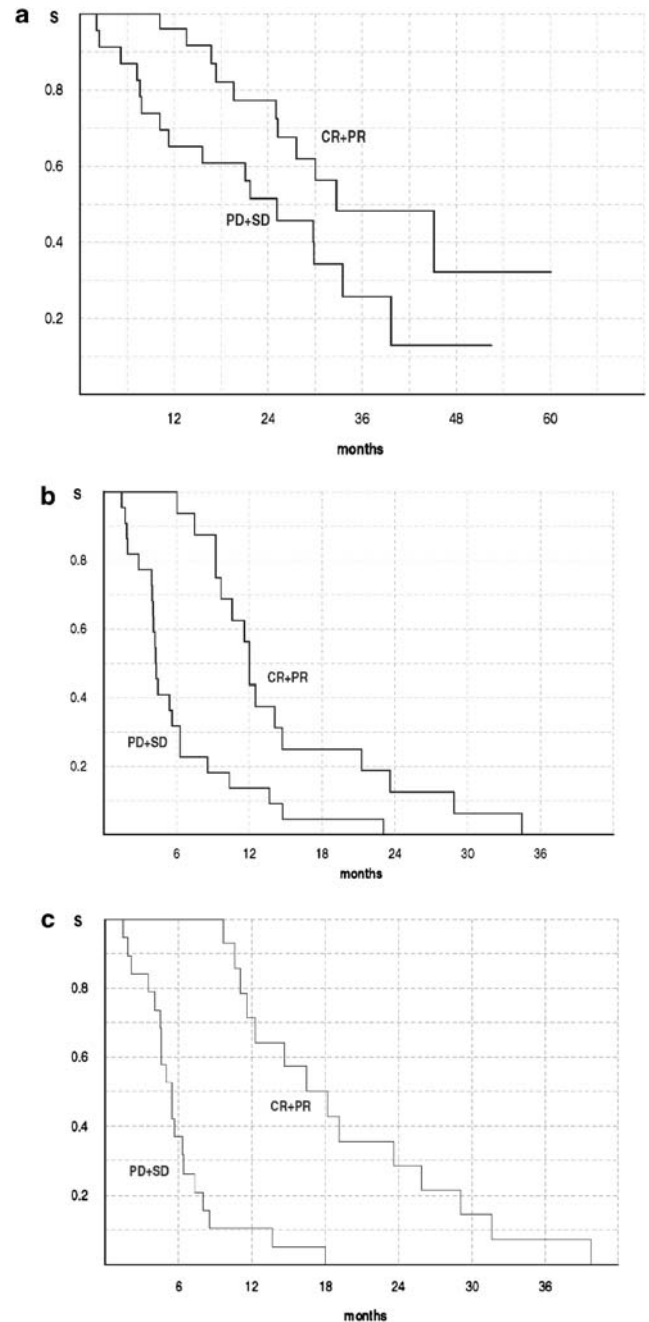

Figure 1 (**a**) Kaplan–Meier OS. Median OS was 30 months (95% CI 25–40 months) with a significant difference ($P = 0.047$) between responders and non-responders. (**b**) Kaplan–Meier estimates of progression-free survival (PFS) based on NCI 1999 criteria. Median overall time to disease progression (TTP) was 8 months (95% CI 5–11 months), with a significant difference ($P = 0.0004$) between responders (median 12 months, 95% CI 10–15 months) and non-responders (median 4 months, 95% CI 4–6 months). (**c**) Kaplan–Meier TTT. Median overall TTT was 9 months (95% CI 6–12 months), with a significant difference ($P < 0.0001$) between responders (median 17 months, 95% CI 12–26 months) and non-responders (median 6 months, 95% CI 4–6 months). OS, overall survival; CR + PR, responders; SD + PD, non-responders; TTP, time to progression; TTT, time to alternative treatment.

1×10^9/l. First dose local reactions were generally mild–moderate, and were limited to injection-site erythema and oedema, which were experienced by 43 patients (88%). Only 10 patients (20.4%) developed a local grade II reaction

Table 3 Relapse and death by response

Characteristic	Total	OR	CR	PR	SD	PD
Relapse or progression, n (%)	38/49 (78%)	16/26 (62.1)	8/13 (61.5)	8/13 (61.5)	17/18 (94.4)	5/5 (100)
Death, n (%)	27/49 (55%)	11/26 (42.3)	5/13 (38.5)	6/13 (46.2)	11/18 (61.1)	5/5 (100)

CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

Table 4 Treatment complications

Haematological toxicity	n (%)
Anaemia	30 (61.2)
Grade I	17 (56.7)
Grade II	12 (40.0)
Grade III	1 (3.3)
Grade IV	0
Neutropenia	36 (73)
Grade I	10 (28)
Grade II	13 (36)
Grade III	7 (19)
Grade IV	6 (17)
Thrombocytopenia	20 (40.8)
Grade I	15 (75.0)
Grade II	2 (10.0)
Grade III	1 (5.0)
Grade IV	2 (10.0)
Non-haematological toxicity	
Injection-site reactions	43 (87.8)
Grade I	33 (76.7)
Grade II	10 (23.3)
Grade III	0
Fever (grade I/II)	14 (28.6)
Polyneuropathy	1 (2.0)
Infections	
Viral reactivations during induction phase	14 (28.4)
CMV	12 (24.4)
HBV	2 (4.0)
Total infections	32 (65)
Infections during induction phase	15 (30.5)
Grade I/II	13 (26)
VZV	3 (6.1)
Fever of unknown origin	6 (12.2)
P. aeruginosa otitis	1 (2)
Localised fungal infections	3 (6)
Grade III/IV	2 (4)
Pneumonia of unknown origin	1 (2)
Aspergillus fumigatus pnemumonia	1 (2)
Infections during 12-month follow-up	15 (30.5)
Grade I/II	7 (14)
Fever of unknown origin	7 (14)
Grade III/IV	8 (16)
Pneumonia of unknown origin	3 (6)
Listeria monocytogenes encephalitis	1 (2.0)
Sepsis of unknown origin	3 (6)
P. aeruginosa sepsis	
Grade III/IV infections (beyond month 12)	
P. carinii pneumonia	1 (2)
H. influenzae pneumonia	2 (4)
Autoimmune complications	
AIHA	4 (50)
ITP	3 (37)
Evans' syndrome	1 (13)

AIHA, autoimmune haemolytic anaemia; HBV, hepatitis B virus; ITP, idiopathic thrombocytopenic purpura.

according to version 2.0 of the National Cancer Institute Common Toxicity Criteria. Almost one-third of the patients experienced low-grade fever at the beginning of treatment, which persisted beyond the first week in only two cases. None of the patients developed any gastrointestinal, hepatic or renal toxicity related to alemtuzumab, although one developed severe sensitive motor peripheral polyneuropathy 6 months after completing the treatment, which was successfully treated with high-dose intravenous immunoglobulins.

Infectious complications were detected in 30 patients: 15 occurred during alemtuzumab treatment and 15 during the 12-month follow-up. Most of the infections recorded during the 4 months of alemtuzumab therapy were grade I/II, with only two episodes of grade IV pulmonary complications arising in patients with PD. Eight of the 15 infections documented during follow-up were severe (four cases of septicemia, three of pneumonia and one of encephalitis); six occurred in patients with PD and two in patients in CR.

Two cases of pneumonia (one because of *Pneumocystis carinii* and one to *Haemophilus influenzae*) were recorded after the 12-month follow-up period (Table 4).

CMV reactivation was detected in one-quarter of the patients during the course of the treatment. In accordance with our pre-emptive strategy, prompt oral ganciclovir therapy was always started in the presence of increasing titres of pp65 antigenemia/CMV DNA, and none of the patients developed clinically relevant CMV illness.

The combination of alemtuzumab with reverse trancriptase inhibitors was well tolerated and effective in inhibiting HBV proliferation. Lamivudine was started together with alemtuzumab in the eight patients with earlier HBV infection. Two of the five patients with occult HBV infection developed HBV DNA reactivation while on alemuzumab, but this was easily controlled by the addition of adefovir dipivoxil to lamivudine.

Alemtuzumab was safely administered to the patients with a earlier history of autoimmune cytopenia. Four episodes of AIHA were recorded (one during alemtuzumab therapy and three during the follow-up period), two of which were *de novo* episodes and two relapses. Three patients (including one with a history of earlier ITP) developed an episode of ITP (one during alemtuzumab therapy). One patient developed Evans' syndrome during follow-up. Evolution to diffuse large B-cell lymphoma was documented in two of the six PR patients who died during the follow-up.

Discussion

The treatment of relapsing/refractory CLL is still a challenge, particularly in patients who are refractory to fludarabine-containing regimens. The activity of alemtuzumab as a single agent has been established in both earlier untreated and relapsing CLL patients, including those with mutations or deletions of the p53 gene,[1,7,13] but there are still a number

of important open questions regarding the optimal use of alemtuzumab and MoAbs in general.

The few initial dose-finding and pharmacokinetic trials of MoAbs were often small, and the current debate concerning the safety and efficacy of MoAb doses in CLL has highlighted the need to reassess the dose–response relationships of many MoAbs.[14,15] Alemtuzumab has been extensively used in the treatment of CLL, but the classic dosing schedule was developed empirically in the absence of sound pharmacokinetics data. The pharmacokinetics of alemtuzumab is quite complex and non-linear, time- and concentration-dependent and varies widely among patients probably as a result of differences in tumour burden. Its rate of elimination correlates directly with white blood cell counts, becoming slower as white blood cell counts decline as a result of the treatment. Using an improved pharmacokinetics model to achieve adequate but not excessive drug exposure should optimise alemtuzumab therapy (and probably that of other MoAbs).[16,17]

On the basis of the classic schedule, patients undergoing intravenous alemtuzumab therapy receive a theoretical total of 1080 mg, divided into individual doses of 30 mg each.

The subcutaneous route of alemtuzumab administration (which was pioneered by researchers at the Karolinska Institute in Sweden) rapidly became almost universally accepted because of the dramatic reduction in the number and severity of first dose side effects, preserved clinical efficacy and the possibility of offering domiciliary self-administration. In 38 earlier untreated patients, the OR rate was 87% (CR 19%, PR 68%), and the time to treatment failure in the responders was 35 + months. In particular, there were high response rates among patients aged >65 years and even those aged >70 years (OR 90%). It is interesting to note that the best bone marrow response was achieved only after 18 weeks of treatment, but was documented in more than 50% of patients.[6] The theoretical total amount of drug delivered on the basis of this protocol is 1620 mg, and the median cumulative dose of alemtuzumab actually administered was 1213 mg.[6]

The efficacy of the subcutaneous route of administration was confirmed in fludarabine-refractory CLL patients by a German CLL Study Group trial designed to assess the relationship between genetic abnormalities and the response to alemtuzumab. The median alemtuzumab dose was 722 mg (range 3–2203 mg), and the OR rate was 36%, median progression-free survival was 9.7 months, and median OS was 13.1 months. Alemtuzumab was effective in terms of OR and OS across all biological risk groups, including those with unmutated IgVH genes or 17p- and/or 11q-.[18]

Montillo et al.[10] showed that low-dose alemtuzumab can be safely used as consolidation therapy in CLL candidates for haematopoietic stem cell autografting, leading to in vivo purging and an improved quality of response to earlier therapy. The patients enrolled in this trial received alemtuzumab 10 mg s.c. three times a week for 6 weeks (cumulative dose 180 mg). On the other hand, alemtuzumab consolidation (30 mg three times per week) was associated with a risk of severe infectious events when it was given shortly after induction therapy,[19] and when it was used after induction therapy including rituximab.[20,21]

In our study, we prospectively explored the possibility of obtaining equally positive results while avoiding untoward effects using a much lower dose of alemtuzumab (a theoretical cumulative dose 540 mg, and a median actual cumulative dose of 480 mg) than the classic dose: that is half cumulative and one-third individual dose.

An initial pilot study of 16 CLL patients showed that this approach was well tolerated and effective,[9] and the final results

of our trial indicated that fairly prolonged but non-aggressive alemtuzumab monotherapy leads to a high OR rate (53%, including 26% of CRs) in patients with advanced and pretreated CLL who had become refractory to their last anti-leukaemic treatment. In line with earlier reported observations,[6] the blood, lymph node and spleen responses were quite rapid, but bone marrow response was slower than that observed using the classic i.v. schedule, thus confirming the need for a longer time of alemtuzumab administration when given subcutaneously.

It is worth pointing out that these results were obtained despite the decreased bioavailability of s.c. administered alemtuzumab,[22] and the fact that we used a substantially lower dose than that used in earlier reported studies involving similar subsets of patients.[1,6,18,23] The responses were equally good regardless of the presence of clinical or biological factors known to have an impact on CLL prognosis, such as and advanced age or clinical stage, an unfavourable karyotype (particularly 17p deletion), CD38 or ZAP70-positive leukaemic cells and refractoriness to alkylating agents and purine analogues. Importantly, in comparison with the patients who did not show a substantial response (that is, those with SD) or who progressed while receiving alemtuzumab, the responders experienced a significantly prolonged TTP (12 vs 4 months) and TTT (17 vs 6 months). Finally, life expectancy also seemed to be affected by a positive result, as the survival of the responders was longer, although the difference was only of borderline statistical significance.

These favourable efficacy results were coupled with a positive toxicity profile. Only a few and short-lived immediate reactions were recorded: albeit frequently observed, injection-site reactions were generally very mild and transient, whereas systemic reactions were notably absent. This low level of local toxicity may have been because of our policy of combining alemtuzumab with low-dose hydrocortisone in the same syringe, even though equally positive tolerability has been described with and without systemic steroid prophylaxis.[6,23]

Although the incidence of CMV reactivation was substantial, it was in line with earlier reports.[4,24] Furthermore, the patients with CMV reactivation showed no clinical signs of CMV disease and, once the CMV had been rapidly cleared be means of pre-emptive oral ganciclovir therapy, they could all safely resume taking alemtuzumab.

The incidence of infectious episodes was also substantial, but once again in line with earlier published data concerning advanced CLL patients treated with alemtuzumab or otherwise.[4,17] There were 30 infectious complications, half of which occurred during treatment and half during the 12-month follow-up: that is 0.6 episodes per patient for the entire observation period. Furthermore, only one-third of the infections was severe or life-threatening (0.2 episodes per patient).

The costs of low-dose therapy are in principle half those of the classic i.v. schedule and less than half of those of full-dose alemtuzumab s.c. for 18 weeks. One technical problem when giving patients 10 mg individual doses is the fact that the current galenic size of alemtuzumab is 30 mg per ampoule. Vermeulen et al.[25] have shown that it is possible to prepare multiple doses of alemtuzumab from a single vial, store them refrigerated and safely administer them within 28 days, with a significant impact on cost. Nevertheless, our experience and that of other authors using low-dose Campath (for example, for maintenance/consolidation) indicates a need for a 10 mg ampoule formulation.

Our experience raises the question of appropriately selecting 'ideal' patients with refractory CLL for low-dose s.c. alemtuzumab treatment. Our study population was highly sensitive to Campath, regardless of the presence of a number of negative

clinical and biological prognostic factors: in particular, neither old age nor advanced clinical stage seemed to be limiting factors, and a very good response was also documented in patients whose leukaemic cells carried the 17p- alteration. However, the majority of our patients (44/49) had a WHO performance status (PS) of <2. Moreover, the response obtained in the five patients with a PS of 2 was very poor: that is one SD and four PDs. The results obtained in the four patients with bulky nodes were also very poor (1 PR and 3 SDs). We therefore fully agree with the conclusions reached by Karlsson *et al.* that the success of alemtuzumab therapy greatly depends on factors such as a good performance status, the absence of bulky lymph nodes and continuing therapy as planned by appropriately managing predictable adverse events.

Taken together, our data can be considered as marking a step towards the easier and less aggressive use of alemtuzumab, and may reduce the fear of adverse effects even in CLL patients who are very old or have pre-treated disease and a poor prognosis.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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