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Alemtuzumab

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Contents

Abstract

▲ Alemtuzumab is an unconjugated, humanised, monoclonal antibody directed against the cell surface antigen CD52 on lymphocytes and monocytes.

▲ In noncomparative phase I/II studies in patients with B-cell chronic lymphocytic leukaemia (B-CLL) relapsed after or refractory to alkylating agents and fludarabine, intravenous (IV) administration of alemtuzumab 30 mg/day three times weekly for up to 12 weeks was associated with overall objective response (OR) rates of 21–59%. Combining alemtuzumab with fludarabine resulted in ORs >80%.

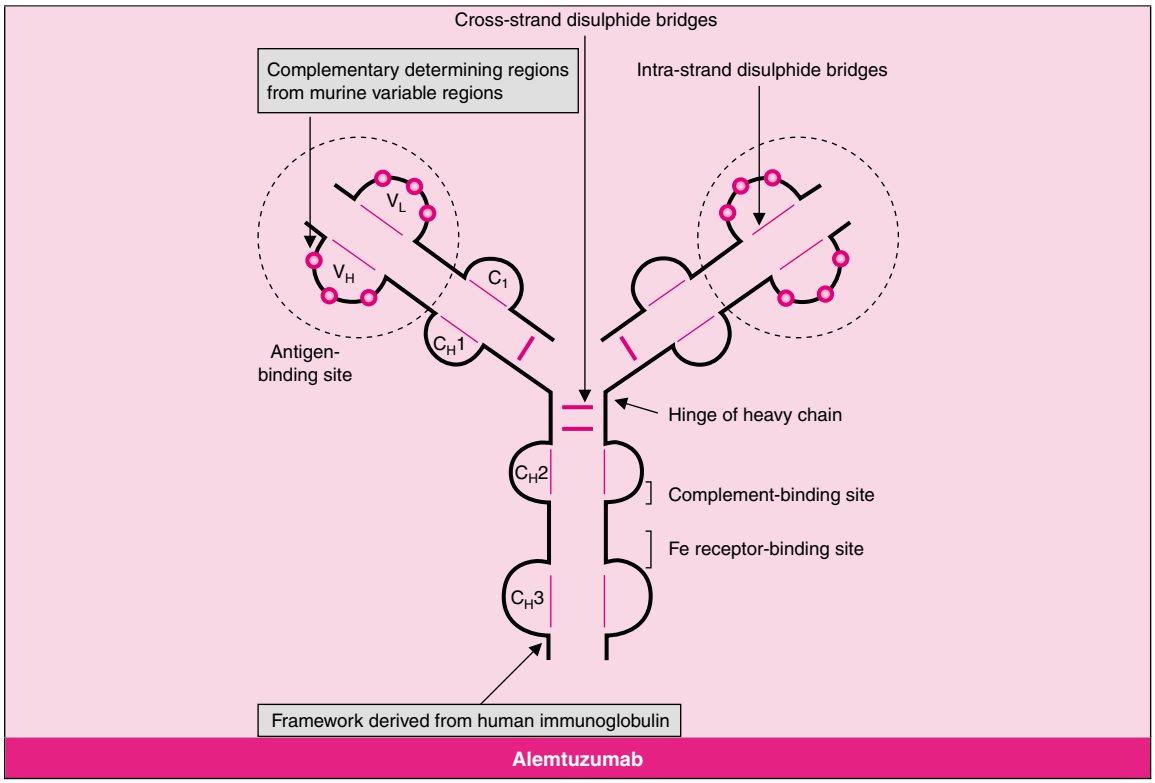
▲ In noncomparative studies in patients with previously untreated B-CLL, subcutaneous (SC) administration of alemtuzumab alone, or IV in combination with fludarabine, was highly effective, achieving OR rates of around 90%.

▲ IV alemtuzumab was active in patients with chemotherapy-resistant/relapsed T-cell prolymphocytic leukaemia, with reported OR rates of 24–76%.

▲ Alemtuzumab has been incorporated in novel conditioning regimens designed to facilitate stem cell transplantation in haematological malignancies.

▲ Adverse events with alemtuzumab are predictable and manageable. 'First-dose' flulike symptoms, frequently seen after IV infusion, can be managed by (pre)medication and minimised by dose escalation (or SC injection). Anti-infective prophylaxis is mandatory. Cytopenias are transient, although red blood cell and platelet support may be required.

Features and properties of alemtuzumab (Campath-1H; Campath®, MabCampath™, humanised anti-CD52 antigen unconjugated monoclonal antibody)	
Indication	
B-cell chronic lymphocytic leukaemia in patients previously treated with alkylating agents and refractory to fludarabine therapy	
Mechanism of action	
Induces lysis of target (CD52 antigen-bearing) lymphocytes and monocytes by antibody-dependent cell-mediated lysis, complement-mediated lysis, and possibly apoptosis	
Dosage and administration (intravenous route)	
Method of administration	2-hour infusion (not push or bolus)
Dosage and frequency of administration	3mg increasing (as tolerated) to 10mg and then 30mg once daily in the first week; thereafter 30 mg/day three times weekly
Duration of administration	12 weeks
Pharmacokinetic profile (intravenous route)	
Peak plasma concentration	26.4 μg/mL
Elimination half-life	12 days
Adverse events	
Acceptable toxicity in context, although 'first-dose' infusion reactions (e.g. rigor, drug-induced fever), infections, and haematological toxicities are potentially serious	



Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia in Europe and the US, accounting for 25–30% of all leukaemias. It is primarily a disease of the aging population; the median age at diagnosis is 64 years, with only 10–15% of patients under the age of 50 years affected.[1-3] In approximately 95% of patients, CLL involves the proliferation and accumulation of mature B cells with a characteristic immunophenotype that includes expression of the surface antigens CD5, CD19, CD20, CD22 and CD52.[1]

Current standard chemotherapy for B-cell CLL (B-CLL), consisting of the alkylating agent chlorambucil and/or the purine analogue fludarabine, induces clinical remission very effectively, although treatment remains palliative rather than curative.[4-6] Historically, the advanced age of patients with B-CLL and rarity of complete marrow remission (pre-fludarabine) has limited, respectively, the application of allogeneic or autologous haematopoietic stem cell transplantation – hitherto the only potentially curative modalities.[2,3,7]

The idea that antibodies can act as anticancer agents ('magic bullets') on account of their ability to recognise (and react with) tumour-associated antigens has been in existence for almost 100 years.[8] Targeted immunotherapy with a new generation of humanised monoclonal antibodies (mAbs) is emerging as an important additional approach to the management of haematological lymphoproliferative malignancies, such as B-CLL and low grade non-Hodgkin's lymphoma (NHL).[7-16] Alemtuzumab (Campath-1H; Campath®[1], Mabcampath™), the focus of this profile, is a humanised anti-CD52 antigen unconjugated mAb.[17] Clinically, it has been investigated for the treatment of various B- and

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

T-cell malignancies, as well as the prevention of graft versus host disease (GVHD) and graft rejection in the setting of stem cell transplantation.

1. Pharmacodynamic Properties

CD52 is a 21–28kD cell surface glycoprotein which is expressed on more than 95% of peripheral blood lymphocytes, tonsillar cells, thymocytes, monocytes and macrophages, but not on granulocytes, platelets, erythrocytes, and haematopoietic stem cells. Membrane-bound antigen is also strongly expressed by most B- and some T-cell malignancies, but by only a minority of myeloid leukaemias.[18-20]

- Alemtuzumab is an unconjugated, nonmodulating, humanised, IgG1 kappa mAb which targets the CD52 antigen. After binding to target (CD52-bearing) cells, it may cause cell death through host-effector mechanisms, such as complement-dependent cytolysis (CDC),[21,22] antibody-dependent cellular cytotoxicity (ADCC)[23,24] and apoptosis.[25,26] Alemtuzumab shares the lympholytic activity of its murine IgM and IgG2b predecessors, but is significantly less immunogenic, thereby facilitating its use clinically.[1,17,27-30]

- In a pivotal study in 93 patients with advanced B-CLL relapsed after or refractory to alkylating agents and fludarabine, intravenous (IV) administration of alemtuzumab (target dose 30 mg/day three times weekly) rapidly eliminated virtually all malignant cells from the peripheral blood. The median number of CD19+/CD5+ lymphocytes was reduced from $33.6 \times 10^3/\mu L$ at baseline to $0.003 \times 10^3/\mu L$ and $0.001 \times 10^3/\mu L$, respectively, after 4 and 12 weeks' treatment (figure 1). The absolute lymphocyte count was also profoundly reduced at week 4 but, unlike the malignant cell count, it began to recover during continued alemtuzumab therapy. A similar pattern was seen in the CD4+ and CD8+ T lymphocyte subset counts.[31]

- In earlier studies in small cohorts of patients (n = 9–18) with various lymphoproliferative disorders (e.g. B-CLL, NHL), alemtuzumab cleared malignant cells from peripheral blood (especially), bone marrow, and the spleen, but had less effect on malignant cells in lymph nodes and extranodal masses.[24,32,33] In one of these early studies, CD19+/CD5+ cells were purged after a median treatment period of 16 (range 7–25) days; they were absent from the blood for >8–>24 months during unmaintained follow-up.[32]

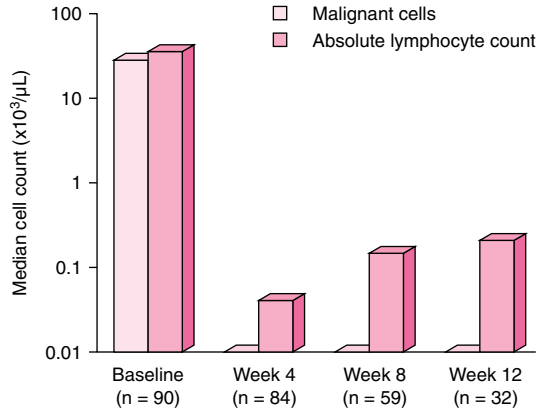


Fig. 1. Effect of alemtuzumab on clonal CD19+/CD5+ lymphocytosis in the peripheral blood of patients with chronic lymphocytic leukaemia (CLL). Absolute lymphocyte and malignant cell counts (estimated from graph) after 4, 8, and 12 weeks' therapy with alemtuzumab 30 mg/day thrice weekly in a pivotal, prospective, non-comparative, phase II study in 93 patients with CLL relapsed after or refractory to alkylating agents and fludarabine.[31] Numbers in parentheses indicate the number of evaluable patients.

- The nonmodulatory nature of alemtuzumab notwithstanding, there are reports of the emergence of populations of CD52 antigen-negative B and/or T lymphocytes,[32,34] including resistant malignant clones,[35] during treatment. In a small study, CD52-negative T (but not B) cells persisted for 4–>19 months during unmaintained follow-up after alemtuzumab therapy.[32]

- *In vitro*, alemtuzumab did not abrogate the ability of CD34+ cells to establish haemopoiesis and to generate haemopoietic progenitor cells, as determined in long-term bone marrow cultures (an assay for putative stem cells).[19] *In vivo*, alemtuzumab therapy did not adversely affect peripheral blood stem cell (PBSC) harvesting or subsequent haematopoietic reconstitution in patients undergoing autologous PBSC transplantation.[36]

2. Pharmacokinetic Properties

A small amount of pharmacokinetic data on alemtuzumab are available from men and women with lymphoproliferative or autoimmune disorders; further relevant studies are ongoing.[17]

- The pharmacokinetics of alemtuzumab administered by IV infusion once weekly for 12 weeks were studied in an escalating-dose trial in patients with B-CLL or NHL.[37] Over a range of doses (not reported), the peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) showed relative dose proportionality. The overall average plasma elimination half-life ($t_{1/2}$) over the dosage interval was ≈12 days.[37] The estimated $t_{1/2}$ after IV administration of alemtuzumab in patients with rheumatoid arthritis was 5–9 days.[38]
- The drug can also be administered by subcutaneous (SC) injection. Maximum plasma concentrations of alemtuzumab were 26.4 and 19.5 mg/mL after administration of 30 mg/day three times weekly for up to 12 weeks by the IV or SC route, respectively, as measured in 50 patients with CLL using a flow cytometry assay.[39] Peak and trough plasma concentrations of the drug rose in line with the reduction in malignant lymphocytes during the first few weeks of treatment with IV alemtuzumab 30 mg/day three times weekly. Steady-state was approached after approximately 6 weeks, although there was marked interpatient variability.[37]
- The mean plasma concentration of alemtuzumab (total cumulative dose 100mg given IV on days −5 to +4 of the transplant) at the time of stem cell infusion in 31 patients undergoing bone marrow transplantation who were cotreated with cyclosporin and methotrexate was 2.3 (range 0.5–3.6) mg/mL; the drug was still detectable 23–85 days post-transplant. These patients were negative for cytomegalovirus (CMV) infection. In contrast, another group of 14 patients who were CMV-positive (and hence at higher risk of developing an infectious complication [see section 4]) received an abbreviated course of alemtuzumab (total cumulative dose 50mg given on days −10 to −6 of the transplant). As expected, the mean plasma concentration at the time of transplantation in this second group was lower (1.2 [range 0.5–3.5] mg/mL) and the drug less persistent (mean 8 [range 1–23] days post-transplant).[40,41]
- Likewise, daily IV infusion of alemtuzumab 20mg over 8 hours on days −8 to −4 of nonmyeloablative allogeneic bone marrow transplantation in 10 patients resulted in a C_{max} value on the day of stem cell infusion of ≈5 mg/mL.[42] Although reduced by at least one-half compared with those after the last infusion (10–30 mg/mL), these levels were still in excess of that required to substantially reduce recipient lymphocyte numbers (0.1 mg/mL).[42]
- Details of the drug's metabolism and excretion are currently unavailable, although the US product labelling states that dosage adjustment is not required in patients with hepatic or renal failure (see section 5).[37]

3. Therapeutic Efficacy

The clinical efficacy of alemtuzumab in lymphoproliferative disorders has been investigated in various patient groups, most notably those with fludarabine-resistant/relapsed B-CLL, but also including those with previously untreated B-CLL and chemotherapy-resistant/relapsed T-cell prolymphocytic leukaemia (T-PLL).

To date, all studies in these various settings have been noncomparative, phase I/II studies; comparative, randomised, double-blind trials demonstrating increased response rates, survival, or clinical benefits such as improvement in disease-related symptoms, have yet to be performed.

B-Cell Chronic Lymphocytic Leukaemia

Most phase I/II clinical trials have assessed IV alemtuzumab alone, or combined with another agent, as salvage therapy in patients with advanced B-CLL who have active disease after prior therapies, including fludarabine. Patients who 'fail' (i.e. relapse after or are refractory to) fludarabine have a poor prognosis, with only approximately 40% surviving beyond 1 year (median survival 8 months).[43] Historically, there were no accepted effective therapies for these individuals;[12] all available treatment

options were experimental (e.g. purine analogue-based combination chemotherapy,[44] mAb therapy, stem cell transplantation).

Similarly, SC alemtuzumab, alone or combined with fludarabine, has been investigated as first-line therapy in previously untreated patients with B-CLL. The perceived advantages for the patient of SC injection as opposed to IV infusion of alemtuzumab are that it may be better tolerated (fewer administration-related side effects [see section 4]) and more convenient (self administration is feasible), while from the healthcare system's perspective it may reduce costs.[45]

General eligibility requirements in clinical trials of alemtuzumab included age ≥18 years and World Health Organization (WHO) performance status (PS) ≤2. Exclusion criteria included previous treatment with alemtuzumab (except where stated), prior transplantation, allergy to hybrid monoclonal antibodies, active infection, active secondary malignancy, CNS involvement, HIV infection or pregnancy/lactation.

Unless otherwise stated, patients received a standard course of alemtuzumab administered by the IV or SC route; this consisted of dose escalation from 3mg to 30mg (usually within the first week) followed by 30 mg/day three times weekly for a minimum of 4 weeks and a maximum of 12–16 weeks (salvage therapy, IV and SC administration) or 18 weeks (first-line therapy, SC administration).

The primary efficacy endpoint was the overall objective response (OR; complete response [CR] plus partial response [PR]) according to 1988[46] or 1996[47] National Cancer Institute (NCI) Working Group (WG) criteria. A CR indicated the absence of clinically and cytologically detectable disease, including from the bone marrow, whereas a PR indicated a >50% reduction in detectable disease.

Salvage Therapy

The effectiveness of IV alemtuzumab as a salvage therapy in patients with advanced B-CLL who were previously treated with alkylating agents and had failed fludarabine therapy has been demonstrated in several single- and multiple-centre, prospective, noncomparative, phase I and II clinical trials (n = 3–93).[31,48-54] Where stated, fludarabine failure was defined as the failure of at least one fludarabine regimen to achieve a CR or PR according to NCIWG guidelines,[47] disease progression while on fludarabine treatment, or disease progression in responders within 6 months of the last dose of fludarabine. The OR rate in these studies was 21–59%, with most patients entering partial clinical remission. Similarly, SC administration of alemtuzumab achieved OR rates of 50% (all PRs) and 62% (CR 31%) in two studies involving a total of 18 evaluable patients from this prognostic group.[55,56]

- In a fully published, multinational, noncomparative, phase II study, IV alemtuzumab (target dose 30 mg/day three times weekly) was administered for a maximum of 12 weeks to 93 patients aged 32–86 years with relapsed or refractory B-CLL who had been exposed to alkylating agents and had failed fludarabine therapy.[31] Forty-three (46%) of the patients had received multiple fludarabine courses, and 8 (9%), 5 (5%), and 30 (32%) patients had been treated four, three, and two times, respectively. Responses were assessed at weeks 4, 8, and 12, and patients were followed up for 34 months.

- The OR rate in this pivotal study was 33% (CR 2%, PR 31%).[31] Responses to alemtuzumab were seen in all prognostic subgroups except in patients with a WHO PS of 2 at baseline, and were similar in patients who had failed treatment or had previously had a short response to fludarabine (see figure 2). Among the 29 patients who had a PR, 6 had a CR except for cytopenia; 5 had a nodular PR. Fifty (54%) patients had stable disease.

- Alemtuzumab substantially reduced disease in the peripheral blood and bone marrow.[31] Sixty-five (83%) of 78 patients with lymphocytosis at baseline, including 26 of 28 responders, had a normal absolute lymphocyte count after treatment, while 22 (26%) of 85 patients with bone marrow involvement, including 15 of 31 responders, had a normal biopsy. Additionally, two (2.6%) patients had a ≥50% reduction in absolute lymphocyte count and seven responders had a ≥50% resolution of disease in bone marrow.

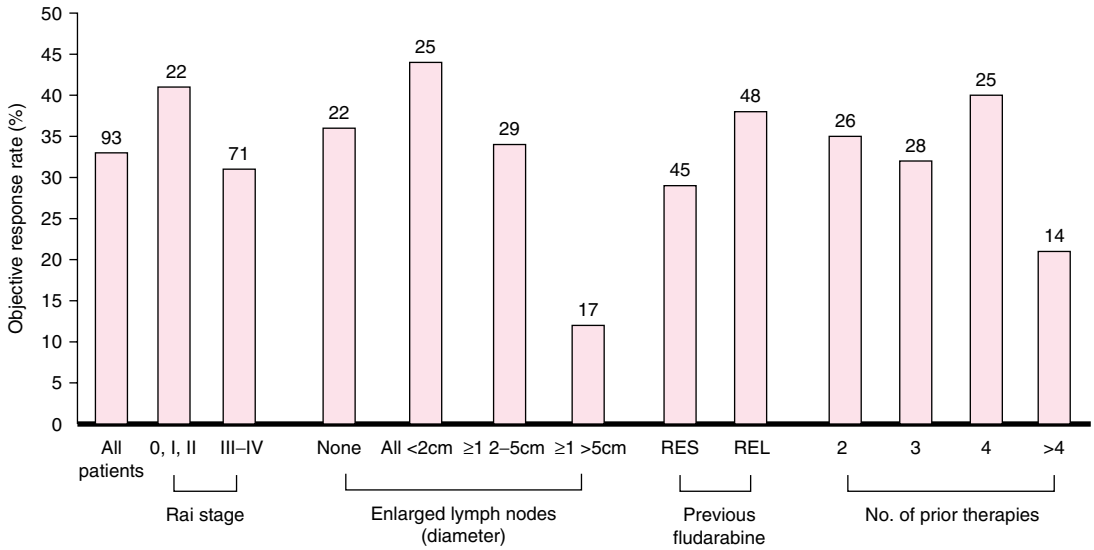


Fig. 2. Efficacy of intravenous alemtuzumab in the treatment of relapsed or refractory B-cell chronic lymphocytic leukaemia (B-CLL). Overall objective (complete plus partial) response rate by selected disease characteristics in a noncomparative study of alemtuzumab 30 mg/day thrice weekly for ≤12 weeks in 93 patients with B-CLL who were previously exposed to alkylating agents and had failed fludarabine therapy.[31] Numbers above bars indicate number of patients. Rai stage classification: **0** = low-risk (early-stage) disease; **I, II** = intermediate-risk disease; **III, IV** = high-risk (advanced-stage) disease; **REL** = relapsed; **RES** = resistant.

- As regards responses at other major disease sites, 18 (27%) of 66 patients with lymphadenopathy at enrollment had complete resolution and 31 (47%) had a ≥50% reduction in enlarged nodes.[31] Twenty-five (54%) of 46 patients with splenomegaly had complete resolution and 13 (28%) had a ≥50% reduction in size of the palpable spleen. Sixteen (52%) of 31 patients with hepatomegaly had complete resolution and 7 (23%) had a ≥50% reduction.

- The median duration of the response to alemtuzumab therapy was 8.7 (range 2.5–>22.6) months and the median time to response was 1.5 (range 0.4–3.7) months (1.8 and 1.2 months for the two complete responders and the 29 partial responders, respectively).[31] The median time to disease progression was 4.7 (range 0.2–>23.6) months overall and 9.5 (range 3–>23.6) months for responders, with three patients (3%) still in clinical remission (response durations >17–>22.6 months) at the data cut-off point.

- At the data cut-off point, 27 (29%) of the 93 patients were still alive, with a median follow-up period of 29 months.[31] Life-expectancy for all patients (median survival 16 months) was twice that of other historical controls (median survival 8 months). Moreover, it was quadrupled in patients who responded to alemtuzumab therapy (median survival 32 months), with 19 (61%) of the 31 responders still alive 21–34 months post-treatment.

- In terms of clinical benefit, B-CLL symptoms or fatigue resolved in 45 (76%) of 59 patients with these symptoms at baseline, including all 17 responders.[31] Similarly, massive splenomegaly (>6cm) was resolved in 16 (55%) of 29 patients affected, including 9 of 10 responders. Improvement in WHO PS status was noted in 17 (25%) of 69 patients who had a WHO PS ≥1 on study entry, including 8 of 20 responders. Improvement in anaemia occurred in 25 (44%) of 57 patients affected, including 11 of 15 responders. Overall, 42 (55%) of 76 patients with various haematological abnormalities at baseline had improvements in at least one cytopenia, including 17 (74%) of 23 responders.

- Prior to the initiation of the pivotal study, two phase II pilot trials of alemtuzumab 30 mg/day three times weekly for up to 16 weeks were performed in

29[48] and 24[50] patients aged 44–77 years previously treated with fludarabine or other chemotherapies. Both of these studies have been published in full.

- Seventeen (71%) of the 24 patients in the smaller study had previously failed fludarabine; the OR rate was 33% (all PRs).[50] Lymphocytosis was normalised in 15 (75%) of 20 patients affected. All 24 patients had lymphocytic infiltration of the bone marrow; this was totally eliminated in 9 (38%) patients. The median duration of the response to alemtuzumab therapy was 15.4 months and the median time to response was 3.9 months. The median time to disease progression was 7.1 months overall compared with 19.6 months in responders. The median survival time was 27.5 months overall compared with 35.8 months in responders.[50]
- The above-mentioned study formed the basis on which a large compassionate-use trial was eventually conducted.[50,57] The efficacy of alemtuzumab 30 mg/day three times weekly for ≤12 weeks in this study of 152 patients with refractory B-CLL, all of whom had failed fludarabine, and some of whom had relapsed after previously responding to alemtuzumab treatment, was similar to that observed in the pivotal trial: the OR rate was 43% (CR 5%, PR 38%). Duration of response and overall survival data on these patients are still being collected.[58]

Multiple and Maintenance Courses

- Data on the efficacy of multiple courses of IV alemtuzumab in patients with relapsed or refractory B-CLL are limited.[59] However, early experience in a total of seven patients suggests that patients continue to respond to repeated courses of standard or modified regimens.[60-62]
- Published as an abstract, preliminary data in 17 patients with refractory lymphoproliferative malignancies (including seven with B-CLL) showed that clinical outcomes on a maintenance regimen of IV alemtuzumab (30 mg/day three times weekly until PR then tapered to 30 mg/month for ≥4 months) compared favourably with those after a standard IV course of 30 mg/day three times weekly for up to 12 weeks.[63] The OR rates were 83% (CR 33%, PR 50%) and 64% (CR 18%, PR 46%) on maintenance and standard therapy, respectively (n = 6 and 11). The median times to disease progression were 12.1 and 3.9 months, respectively. Median survival times were >16.7 and 5.3 months, respectively.[63]

Combination Therapy

- In two early studies, one of which has been published in full,[64] combination therapy with IV alemtuzumab (total of seven 30mg doses over 4 weeks) plus the anti-CD20 antigen mAb, rituximab, yielded encouraging results in patients with relapsed or refractory B-CLL expressing both the CD52 and CD20 antigens.[65,66] A phase II trial evaluating the clinical efficacy of the combination in this setting is currently underway.[64,67]
- Likewise, the seemingly synergistic benefits of combining fludarabine with IV alemtuzumab in patients with relapsed or refractory B-CLL are being assessed in two ongoing phase II studies.[68,69] Findings to date in one of these studies have been published as an abstract.[68] Eleven evaluable patients with relapsed/refractory B-CLL received four 28-day cycles of combined IV fludarabine 30 mg/m^2/day plus alemtuzumab 30 mg/day on days 1–3 of each cycle; the OR rate was 82% (CR 73%, PR 9%).[68] The results of the other pilot study have been fully published.[69] Five (83%) of 6 patients previously refractory to either agent administered singly responded to the combination, including one who had a CR.[69]

Consolidation Therapy

- In two preliminary studies, IV[70] or SC[71,72] administration of alemtuzumab further increased the CR rate in patients with B-CLL, the majority of whom were previously untreated, who responded to tumour debulking with fludarabine.
- In the largest study, published as an abstract, 56 patients received first-line therapy with IV fludarabine 25 mg/m^2/day 5 consecutive days a month for 4 months; those who had stable or better disease went on to receive IV alemtuzumab (target dose 30 mg/day three times weekly) for 6 weeks.[70] The OR rate after the fludarabine phase was 56% (CR 4% [n = 2], PR 52% [n = 29]); this increased to 92% (CR 42% [n = 15], PR 50% [n = 18]) among the 36 patients who subsequently entered the alemtuzumab phase.[70]

• The smaller study involved 12 patients with minimal residual disease (MRD) after fludarabine therapy; following full publication of the first results,[72] this trial was recently updated in an abstract.[71] Two patients were already in complete clinical remission; of the remaining ten, four who exhibited a partial clinical remission and 5 of 6 who exhibited a nodal partial remission following fludarabine achieved a complete clinical remission after SC administration of alemtuzumab in escalating doses of up to 10mg three times weekly for 6 weeks.[71]

• Four of the original 12 patients in this study achieved a molecular complete remission (i.e. no detectable disease as determined by sensitive techniques such as flow cytometry and/or polymerase chain reaction [PCR] amplification) and 6 converted into morphological and immunophenotypic complete remission after alemtuzumab therapy.[71] Achieving molecular (as opposed to clinical) complete remission is associated with improved survival, reduced likelihood of relapse (i.e. more durable response), and is becoming the therapeutic goal in B-CLL, particularly for younger patients.[59]

First-Line Therapy

• In a fully published, noncomparative, phase II trial,[45] self-administered SC alemtuzumab (target dose 30 mg/day three times weekly) for a maximum of 18 weeks was highly effective as a first-line treatment for B-CLL, reinforcing the results of a pilot study in nine patients.[73] Thirty-eight evaluable, untreated symptomatic patients received ≥4 weeks' alemtuzumab therapy, with an OR rate of 87% (CR 19%, PR 68%). At the time of reporting, the median time to treatment failure had not been reached (>18 [range 7–>44] months).[45]

• Alemtuzumab effectively eradicated malignant cells in the blood and bone marrow. Ninety-five percent of patients had their blood completely cleared of malignant cells, and 66% showed complete or close to complete morphologic remission of disease in bone marrow. Additionally, 2% and 13% of patients had partial resolution of disease in the blood and bone marrow, respectively. Eighty-seven percent of patients with lymphadenopathy (n = 31) had a response, including 29% with complete resolution. Similarly, 90% of patients with splenomegaly (n = 28) had a response, including 36% with complete resolution.[45]

Post-Thymic T-Cell Malignancies

T-Cell Prolymphocytic Leukaemia

T-PLL is an aggressive disease affecting mainly adults (median age at diagnosis is 63 years); it accounts for approximately 3% of all T-lymphocyte disorders. Often resistant to conventional chemotherapy, T-PLL has a poor prognosis: median survival was 7.5 months in one historical series.[74-76]

• The effectiveness of IV alemtuzumab in patients with refractory T-PLL has been demonstrated in four noncomparative trials (n = 12–76).[20,58,77,78] The OR rates in these studies were 24–76%, with most patients entering complete remission.

• The largest series to date consisted of 76 compassionately-treated patients, 72 of whom had failed at least one chemotherapy regimen.[78] The general eligibility/exclusion criteria, alemtuzumab dosage regimen, and efficacy endpoints in this fully published retrospective analysis were similar to those for the B-CLL studies. Also included were 18 patients from an earlier smaller series (n = 39) which reported a very high OR rate (76% [CR 60%, PR 16%]) and prolonged median survival in CR patients (16 months vs 9 months and 4 months in PR and nonresponding patients, respectively; p = 0.0007).[77]

• Among the 72 pretreated patients in this study, the OR rate was 50% (CR 37.5%, PR 12.5%). Among all 76 patients, the median duration of CR was 8.7 (range >0.1–44.4) months and the median time to disease progression was 4.5 (range 0.1–45.4) months; the latter was longer than that observed with prior first-line chemotherapy (2.3 [range 0.2–28]) months. Median survival at the data cut-off date was 7.5 months for all patients and 14.8 months for CR patients.[78]

• The results of a second, smaller compassionate-use study in 29 patients with T-PLL were published as an abstract; the OR rate was 24% (CR 14%, PR

10%).[58] Duration of response and overall survival data on these patients are still being collected.[58]

Other T-Cell Malignancies

- Intravenous alemtuzumab 30 mg/day three times weekly for up to 12 weeks showed promising activity in 22 patients with advanced cutaneous T-cell lymphoma (mycosis fungoides/Sezary syndrome), most of whom had stage III–IV disease.[79] The OR rates were 55% (CR 32%, PR 23%) overall, 69% for erythroderma, and 40% for plaque or skin tumours. Patients also reported a reduction in itching.[79] Similarly, alemtuzumab therapy produced an OR of 50% (CR 25%, PR 25%) in a subgroup of 8 patients with mycosis fungoides as part of a study of 50 patients with chemotherapy-resistant/relapsed advanced low-grade NHL.[80]

Stem Cell Transplantation

Although allogeneic stem cell transplantation following myelablative chemotherapy for CLL is associated with a higher rate of treatment-related mortality compared with autologous transplantation (25–50% vs 4–19%), it results in improved survival (plateauing at 40–60%, with 10–25% patients relapsing) on account of an additional 'graft-versus leukaemia' (GVL) effect (see review by Schriever and Huhn[9]).

Allogeneic Transplantation

Historically, GVHD was a significant cause of morbidity and mortality after allogeneic bone marrow transplantation despite the best immunosuppressive therapy.[81] However, the incidence of GVHD can be reduced by depleting donor T cells with alemtuzumab, which is added to the stem cells 'in the bag' or infused into the recipient around the time of transplantation (see reviews by Hale[82] and Hale et al.[83,84]).

- Both *ex vivo*[81,85-88] and *in vivo*[89,90] administration of alemtuzumab were effective in reducing GVHD and graft rejection mediated by donor and recipient T cells, respectively. In a series of 187 patients who received PBSC transplants from HLA-matched siblings, the risk of acute grade 2–4 GVHD after *ex vivo* addition of alemtuzumab (or its murine IgG2b predecessor) 10–120 mg/L was 4%, of chronic any grade GVHD was 24%, and of extensive chronic GVHD was 2%. The overall risk of graft rejection was 2%. At 1 year, transplant-related mortality was 22%.[81]
- Pretransplant administration of alemtuzumab has also been shown to deplete circulating host antigen-presenting dendritic cells,[91,92] an effect that could contribute, in part, to the prevention of GVHD.[82,92]
- One innovative strategy, incorporating nonmyeloablative as opposed to myeloablative conditioning, has revolutionised allogeneic transplantation, extending its availability to patients previously excluded on account of advanced age or comorbidity.[93] In a series of 44 patients with high-risk leukaemia/lymphoma who underwent allogeneic transplantation, alemtuzumab 20 mg/day (on pre-transplant days 8–4) was added to nonmyeloablative conditioning using IV fludarabine 30 mg/m^2 (on pre-transplant days 7–3) and melphalan 140 mg/m^2 (on pre-transplant day 2).[89] Forty-two (98%) of the 43 evaluable patients had sustained engraftment. Only two patients developed acute grade 2–4 GVHD; one patient had chronic GVHD. After a median follow-up of 9 months, 33 patients remained alive in complete remission or with no evidence of disease progression. Estimated overall survival at 1 year was 73%, with 11% non-relapse mortality.[89]

Autologous Transplantation

The aim of conditioning therapy prior to autografting for CLL is to maximally eradicate malignant cells from peripheral blood and bone marrow, thereby minimising the reinfusion of contaminating leukaemic cells. By further eradicating or completely clearing B-CLL cells from these sites in patients with active or residual disease after prior therapies,[31,50,71,94] alemtuzumab may permit further treatment by autologous PBSC transplantation;[59] this has already been performed in a small number of individuals.[95,96]

- In one study, 10 (34%) of 29 patients with B-CLL refractory to purine analogue therapy achieved a CR after additional alemtuzumab therapy; of these, 5 had molecular complete remission and 5 had malignant cells detectable by flow cytometry. Seven

responding patients received autologous PBSC transplantation; of these, 6 were still alive at a median of 10 months post-PBSC transplantation without requiring further therapy.[96]

- In another study, 5 (83%) of 6 patients with residual disease following maximal treatment with purine analogues achieved haematological and histological complete remission after additional alemtuzumab therapy. Uncontaminated stem cells were harvested in three cases; the two remaining patients with contaminated cells proceeded to autologous transplantation without complications and with rapid haemopoietic engraftment.[95]

4. Tolerability

The toxicity of alemtuzumab is predictable and manageable; it is considered acceptable in the context of malignant disease.[1,17,97] Adverse events include acute 'first-dose' administration-related reactions (attributed to antibody-induced cytokine release), infectious complications (due to immunosuppression) and haematological toxicities. Except where stated, the following tolerability profile is based on the results of the pivotal trial in which IV alemtuzumab was administered to 93 patients with B-CLL who had relapsed after or were refractory to treatment with alkylating agents and fludarabine (see section 3).

Infusion-Related Events

- Rigor, fever, nausea, vomiting, skin rash, dyspnoea, and hypotension are among the most commonly reported infusion-related reactions with alemtuzumab[37] (see figure 3); the incidences of these events in the pivotal trial were 90% (14% severe or life-threatening by NCI-Common Toxicity Criteria), 85% (20%), 53% (0%), 38% (1%), 33% (0%), 28% (12%), and 17% (2%), respectively.[31] Six (6%) patients in this study discontinued the drug due to infusion-related adverse reactions.[37]
- The most common of these administration-related reactions manifest as a 'flu-like' syndrome.[1] They mainly occur during the first alemtuzumab infusion and usually decrease in intensity and/or frequency during subsequent infusions. They can also be minimised by dose-escalation and managed by pretreatment with oral antihistamines, paracetamol, and corticosteroids[1,28,97-99] (section 5).
- Premedication in the pivotal trial consisted of diphenhydramine 50mg and acetaminophen 650mg, 30 minutes prior to alemtuzumab infusion. Except for skin rashes, there was a substantial decrease in the incidence of infusion-related reactions (including severe or life-threatening events) from week 1 to weeks 2–4, with a further decrease beyond week 4.[31]
- Flu-like symptoms are reportedly reduced in severity in patients receiving SC injections of alemtuzumab, while other infusion-related events normally associated with IV administration occur only rarely (see review by Rai & Hallek[59]). Instead, most patients develop transient injection-site skin reactions of mild to moderate severity during weeks 1–2 of SC treatment; this requires individual dose escalation that is slower compared to IV administration.[45]

Haematological Toxicity and Infectious Complications

In most phase I/II noncomparative clinical trials, alemtuzumab has been given to heavily pretreated patients with advanced B-CLL who have failed fludarabine. These individuals are already highly susceptible to infection[98] and often have low blood counts prior to initiating alemtuzumab therapy;[99] this could lead to overstatement of the infectious and haematological toxicities of the drug under these conditions. According to one retrospective review (n = 27), the frequency of serious infections in patients with fludarabine-refractory CLL/small lymphocytic leukaemia (SLL) was 89%, even in the absence of further treatment.[100] In the pivotal trial, 76 (82%) of the 93 patients with B-CLL who had failed fludarabine had various cytopenias (anaemia, neutropenia, thrombocytopenia) at enrollment.[31]

Infectious Complications

Lymphopenia, a direct consequence of the pharmacological action of the drug (see section 1), is the most consistent haematological alteration caused by

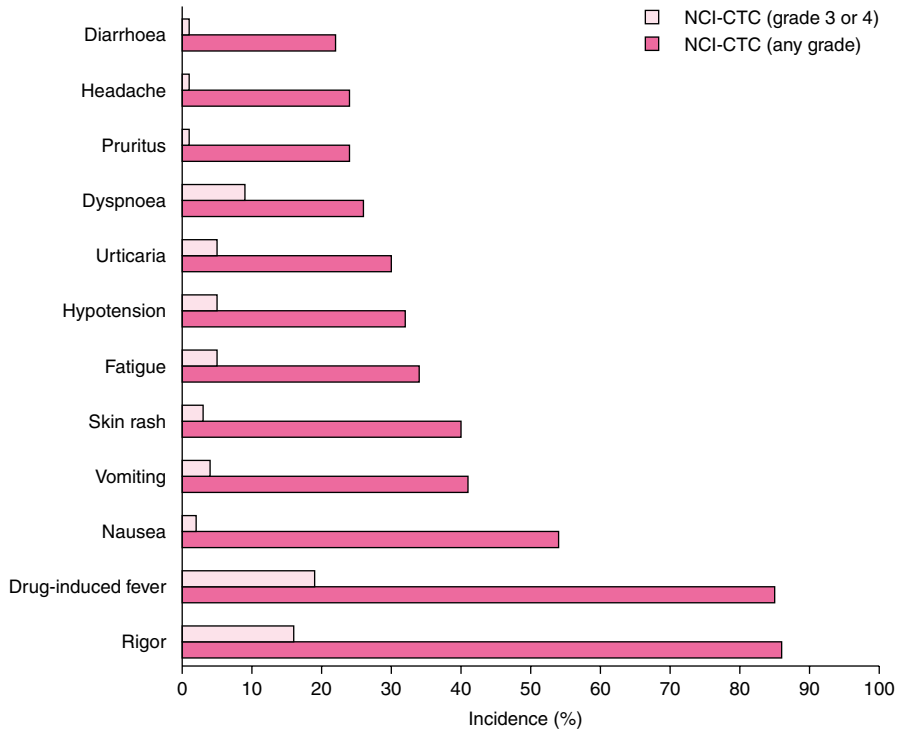


Fig. 3. Infusion-related toxicity of alemtuzumab. Combined incidence of commonly reported administration-related reactions in a total of 149 patients who received alemtuzumab (target dose 30 mg/day thrice weekly) for ≤12 weeks in three similarly designed noncomparative studies.[37] The events listed occurred during or within 30 days of alemtuzumab treatment. **NCI-CTC** = National Cancer Institute-Common Toxicity Criteria.

alemtuzumab; the ensuing period of immunosuppression, which can last for several months after the cessation of treatment, leads to an increased susceptibility to infections.[1] Anti-infective prophylaxis is therefore mandatory during and after alemtuzumab therapy,[1] and consisted of sulfamethoxazole/trimethoprim and famciclovir (or equivalent antiviral regimen) in the pivotal study.[31] Famciclovir does not prevent CMV reactivation, the most frequent opportunistic infection observed,[31,101] although most patients respond rapidly to intravenous ganciclovir.[31,45]

- Fifty-one (55%) of the 93 patients in the pivotal study experienced one or more infections, which were severe or life-threatening in 25 patients. Septicaemia occurred in 14 patients (15%), including 10 (10%) for whom it was severe or life-threatening. Eleven patients experienced opportunistic infections, including seven, six, and four patients with CMV, herpes simplex, and herpes zoster reactivation, respectively, and one each with *Pneumocystis carinii* pneumonia (no prophylaxis administered as per protocol), aspergillus pneumonia, fatal rhinocerebral mucormycosis, systemic candidiasis, fatal cryptococcal pneumonia, fatal pulmonary aspergillosis, and *Listeria monocytogenes* meningitis.[31]
- A retrospective analysis of 1538 patients treated with alemtuzumab for a variety of lymphoid malignancies found the overall incidence of symptomatic CMV complications (infection and/or reactivation) to be 3.6% in the absence of specific CMV prophylaxis. Nine (0.6%) patients had CMV pneumonia and there were three deaths.[102]

Haematological Alterations

- Most patients in the pivotal study experienced transient cytopenias during treatment with alemtuzumab.[31] Thrombocytopenia and neutropenia

were most common during weeks 2 and 5–6 of therapy, respectively, but both had resolved in the majority of patients by the second month of post-treatment follow-up.[31]

- According to the US product labelling,[37] 65 (70%), 48 (52%), and 44 (47%) patients in this study experienced one or more episodes of WHO grade III or IV neutropenia, thrombocytopenia, and anaemia, respectively. Serious neutropenia and thrombocytopenia lasted for a median of 28 and 21 (range for both 2–165) days. Sixty-two (67%) patients required red blood cells for anaemia, and 35 (38%) patients required platelets for thrombocytopenia. Six (6%) patients discontinued treatment because of pancytopenia/marrow hypoplasia, of which two (2%) patients died.[37]
- Results similar to those in the pivotal trial were reported in a study of 43 previously untreated patients with B-CLL who received SC alemtuzumab (target dose 30mg thrice weekly) for up to 18 weeks.[56] The median durations of thrombocytopenia and neutropenia were 26 (range 14–38) and 28 (range 7–128) days, respectively; all patients achieved normal levels within 2 months following therapy. However, cytopenias were reportedly more frequent and slower to recover in 13 heavily pretreated patients who received SC alemtuzumab for up to 12 weeks in this study. Overall, haematological recovery was achieved without the aid of growth factors in most (86%) patients.[56]

5. Dosage and Administration

- As a salvage treatment for B-CLL, the recommended starting dosage of alemtuzumab is 3 mg/day, administered by IV infusion over 2 hours, increasing to 10 mg/day as tolerated.[37] The maintenance dosage of 30 mg/day administered three times weekly on alternate days (maximum 90 mg/week) may be initiated once the 10 mg/day dosage is tolerated (usually after 3–7 days); ideally, treatment should continue for a full 12 weeks.[37]
- Prior to the first dose of alemtuzumab, and at each dose escalation, patients should be premedicated with an oral antihistamine (e.g. diphenhydramine) and acetaminophen to reduce the risk of infusion-related reactions.[37] Corticosteroids (e.g. hydrocortisone) can be used to prevent or ameliorate severe administration-related events when they occur. Alemtuzumab should be temporarily discontinued in the event of serious toxicity until the event has resolved. If therapy is interrupted for ≥7 days, alemtuzumab should be reinstituted with gradual dose escalation.[37]
- Patients must also receive anti-infective prophylaxis (e.g. with sulfamethoxazole/trimethoprim and famciclovir or an equivalent antiviral regimen) to reduce the risk of serious opportunistic infection.[37] The prophylaxis should continue for ≥2 months or until the CD4+ T-cell count is ≥200 cells/μL. Alemtuzumab therapy should be temporarily discontinued in the event of a serious infection until it has resolved.[37]
- Complete blood counts and platelet counts should be obtained at least weekly. Alemtuzumab therapy should be temporarily discontinued in the event of haematological toxicity; recommendations for reinstitution of treatment are provided in the package insert.[37] However, treatment should be stopped permanently if evidence of autoimmune anaemia or thrombocytopenia appears.[37]
- Dosage adjustment is not required in patients with hepatic or renal impairment.[37]

6. Alemtuzumab: Current Status

Alemtuzumab, administered by the IV route, is approved in the US and Europe for the treatment of patients with B-CLL who have been treated with alkylating agents and have failed fludarabine therapy. In both areas, the approval was conditional on the manufacturer conducting a confirmatory phase III trial; this study will compare alemtuzumab with chlorambucil, the standard first-line treatment for CLL, in 284 previously untreated patients with progressing disease.[1] The use of alemtuzumab as a SC injection is also being evaluated in several ongoing studies.

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