

Alemtuzumab: What Is the Secret to Safe Therapy?

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Keywords

Alemtuzumab, chronic lymphocytic leukemia, fludarabine, minimal residual disease, monoclonal antibody

Abstract: Over the past decade, the use of the monoclonal antibody alemtuzumab in chronic lymphocytic leukemia has expanded from administration as a single-agent therapy, into use in combination with fludarabine or rituximab, and further to use as a consolidation agent with the goal of eradicating minimal residual disease. Numerous clinical studies have shown that alemtuzumab is effective as first-line treatment and in patients who have relapsed disease or who are refractory to fludarabine. Despite improvements in response rates and survival compared with combination chemotherapy, there remains some hesitation to incorporate alemtuzumab into management because of known toxicities. Adverse events in patients treated with standard-dose, single-agent alemtuzumab occur at generally predictable time points during treatment and can be managed effectively; this outcome is less established when alemtuzumab is incorporated into combination regimens. Variability in alemtuzumab dosing, route of administration, and duration of therapy has led to inconsistent and sometimes adverse safety consequences. This article presents an overview of clinical studies with alemtuzumab as a single agent, in combination, or in consolidation, with discussion of toxicity and suggestions for ensuring that the efficacious outcomes following alemtuzumab therapy are not outweighed by safety concerns.

Introduction

Current treatments for patients with chronic lymphocytic leukemia (CLL) include a broad range of chemotherapeutic and immunotherapeutic options. These options range from single agents—such as alkylating drugs (eg, chlorambucil), purine analogs (eg, fludarabine, pentostatin, and cladribine, bendamustine [Treanda, Cephalon]), and monoclonal antibodies (eg, rituximab [Rituxan, Genentech/Biogen Idec] and alemtuzumab [Campath, Genzyme])—to combination chemotherapy, immunotherapy, or chemoimmunotherapy.¹ Immunotherapeutic choices for CLL (eg, alemtuzumab, rituximab) provide a more targeted approach that, when combined with chemotherapy, demonstrates significantly improved patient outcomes

compared with chemotherapy alone. This review focuses on the immunotherapy agent alemtuzumab, a monoclonal antibody that targets CD52-positive cells and is currently approved for use as a single agent in B-cell CLL.²

Alemtuzumab first received its indication in patients who had failed prior fludarabine therapy. In a multicenter, phase II study, patients given alemtuzumab achieved a 33% overall response and 16-month median overall survival.³ One additional phase III study of alemtuzumab has led to its expanded indication in the first-line setting, as a result of significantly improved efficacy endpoints over the standard first-line treatment chlorambucil.⁴ Combination studies with fludarabine also demonstrate enhanced patient response with the addition of alemtuzumab in relapsed or refractory disease.^{5,6}

The efficacy of alemtuzumab is often negatively affected by known safety issues associated with treatment. As discussed in this review, the safety profile of single-agent, standard-dose alemtuzumab is predictable overall, and response to treatment is fairly consistent across clinical studies with standard dosing regimens. This outcome has been reiterated by physicians experienced with using alemtuzumab therapy over the past decade; management guidelines are consistently updated to ensure appropriate use of alemtuzumab.^{7,8} Their collective knowledge and practical experience have combined with emerging clinical study results to ensure appropriate guidance based on current treatment practices. Adverse events in patients treated with standard-dose, single-agent alemtuzumab generally occur at foreseeable time points during treatment and can be managed effectively to ensure maximal treatment with the goal of eradicating minimal residual disease. Because minimal residual disease is a major cause of relapse, its eradication is a critical achievement in the treatment of CLL. Patients receiving combination therapy containing alemtuzumab, however, demonstrate less consistent toxicity profiles, requiring further evaluation and standardization of dosing, administration route, and other factors to ensure an optimal risk-to-benefit ratio.

Proposed Treatment Guidelines for Alemtuzumab in CLL

The recommended position of alemtuzumab in treatment guidelines for each line of CLL therapy varies worldwide. Proposed treatment guidelines for patients with CLL were presented by the German CLL Study Group (GCLLSG) at the American Society of Hematology (ASH) meeting in December 2009.¹ These guidelines recommend using alemtuzumab as a single agent or combined with fludarabine as first-line therapy in advanced-stage CLL for patients with poor-prognosis cytogenetics (ie, 17p deletion; Table 1). Alemtuzumab

is the only drug approved by the US Food and Drug Administration that has reported activity for patients with leukemia cells that lack p53 function.

In the early relapsed or refractory setting, alemtuzumab alone or with fludarabine is recommended as standard therapy regardless of a patient's molecular cytogenetic status. The GCLLSG guidelines propose alemtuzumab use early in the course of CLL treatment to improve overall disease management by eradicating minimal residual disease in the earliest possible course of therapy.¹ Per the National Comprehensive Cancer Network (NCCN) guidelines, alemtuzumab used either as a monotherapy or within a combination regimen is a possible therapeutic option, but it is ranked behind a number of other chemotherapy/chemoimmunotherapy combination regimens (Table 1).⁹ Both sets of proposed guidelines give patients with good performance status the option of proceeding to allogeneic stem cell transplantation following combination therapy.

Alemtuzumab Dosing and Clinical Studies

The standard dosing schema for single-agent alemtuzumab is 30 mg/day (following initial dose escalation to minimize infusion-related toxicity) administered 3 times per week for up to 12 weeks.² In relapsed or refractory CLL, standard-dose alemtuzumab monotherapy (intravenous [IV] or subcutaneous [SC]) given for 12 weeks consistently demonstrated 31–42% overall response rates (ORRs) and a complete response (CR) rate of 6% or less.^{3,10-13} Extended treatment at 30 mg for up to 16 weeks or low-dose (10 mg 3 times per week) alemtuzumab showed similar or improved responses compared with standard-dose alemtuzumab monotherapy.¹⁴⁻¹⁷ Activity was demonstrated in fludarabine-refractory patients, as well as in those with 17p deletion and/or p53 mutations. In the first-line setting, standard-dose alemtuzumab achieved improved ORRs of 83–87% (19–24% CR).^{4,18} These early studies established standard dosing for alemtuzumab monotherapy. More recent studies have extended alemtuzumab into the first-line setting and have shown similar efficacy with IV or SC routes of administration, as discussed below.

The CAM307 and CLL2H studies of single-agent, standard-dose alemtuzumab showed responses and remission durations consistent with those in earlier phase II studies of standard-dose alemtuzumab.^{4,13} The CAM307 trial was the pivotal study of alemtuzumab (vs chlorambucil) for first-line treatment of CLL, leading to an expanded indication for first-line alemtuzumab.⁴ Patients receiving standard-dose IV alemtuzumab compared with oral chlorambucil (40 mg/m² every 28 days, ≤12 cycles) showed superior ORR (83% vs 55%, respectively;

Table 1. Current Recommendations for Use of Alemtuzumab-Containing Regimens

	ASH Education Book GCLLSG ¹	NCCN Guidelines ⁹
First-line		
No deleted 17p	Not recommended*	Alemtuzumab [†]
With deleted 17p	Alemtuzumab or Fludarabine plus alemtuzumab	CFAR (FCR + alemtuzumab) combination or Alemtuzumab [†]
Second-line		
No deleted 17p	Standard therapy regardless of molecular cytogenetics Alemtuzumab alone or with fludarabine (early relapse of <1 year; good performance or relevant comorbidities)	Fludarabine plus alemtuzumab: for patients with a short remission (<1–2 years), age <70 years, or good performance Alemtuzumab plus rituximab: when literature exists to support the combination
With deleted 17p	Repeat first-line therapy (late relapse of >1 year)	CFAR (FCR + alemtuzumab) combination Alemtuzumab plus rituximab: when literature exists to support the combination

*Recommended treatments for patients lacking deleted 17p include FCR or fludarabine plus cyclophosphamide.

[†]Less effective for patients with bulky disease (>5 cm) and necessitates cytomegalovirus reactivation monitoring.

ASH=American Society of Hematology; FCR=fludarabine, cyclophosphamide, and rituximab; GCLLSG=German CLL Study Group; NCCN=National Comprehensive Cancer Network.

$P<.0001$), CR (24% vs 2%, respectively; $P<.0001$), and progression-free survival (PFS; 14.6 vs 11.7 months, respectively; $P=.0001$), and prolonged median time to alternative treatment (23.3 vs 14.7 months, respectively).

In the CLL2H study of 103 relapsed or refractory CLL patients, alemtuzumab administered intravenously or subcutaneously achieved a 34% ORR (4% CR), with stable disease in 38% of patients.¹³ At a median follow-up of 37.9 months, median PFS was 7.7 months (95% confidence interval [CI], 5.1–10.0 months), OS was 19.1 months (95% CI, 15.8–29.0 months), and time to treatment failure was 5.6 months (95% CI, 4.4–8.9 months). Patient outcomes were similar regardless of genetic status (eg, 17p deletion, unmutated *VH*) or route of administration (IV vs SC). SC delivery was more convenient for patients; nearly all patients (96%) received the dosage on an outpatient basis. SC administration also showed an improved safety profile in terms of infusion-related skin reactions, and it provided a more cost-effective and flexible delivery mechanism. Both CAM307 and CLL2H showed consistent grade 3/4 adverse events stemming from the use of standard-dose alemtuzumab (Table 2).^{4,13} Toxicity was predictable and manageable, with milder infusion-related adverse events in the first-line setting, as well as after SC administration.

Studies of Combination Regimens With Alemtuzumab

Combination chemotherapy, immunotherapy, or chemoimmunotherapy regimens are increasingly becoming more common therapeutic choices for patients with CLL. A number of combination regimens have included alemtuzumab because of its cytotoxic activity independent of p53 pathways; this provides effective cytotoxic activity independent of poor-prognosis molecular cytogenetics (eg, 17p deletion).^{19,20} Translation of standard-dose, single-agent alemtuzumab into combination regimens has led to variable responses to treatment and alteration of the anticipated toxicity profile.

Initial investigations combined alemtuzumab and fludarabine based on synergistic activity demonstrated in vitro and in small clinical studies.^{5,21} These 2 agents have provided the foundation for a number of other investigated chemoimmunotherapy combinations in CLL, including alemtuzumab plus fludarabine (Flu-Cam)^{5,6,22,23}; fludarabine, cyclophosphamide, and alemtuzumab (FCCam)^{24,26}; and cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR; Table 3).^{27,28} Differences in line of therapy, dosing schema, administration route, and duration of therapy have led to some

Table 2. Major Grade 3/4 Adverse Events in CAM307 and CLL2H Studies of Single-Agent Alemtuzumab

Clinical Study	Adverse Events
CAM307 (N=149) First-line IV alemtuzumab* Hillmen et al ⁴	Grade 3/4 myelosuppression –Neutropenia (60 patients, 41%; febrile in 4.8%) –Thrombocytopenia (18 patients, 12%) –Anemia (16 patients, 11%) Injection-site reactions (12 patients, 8.2%) CMV reactivation (6 patients, 4%, asymptomatic and symptomatic)
CLL2H (N=103) Fludarabine-refractory patients IV or SC alemtuzumab Stilgenbauer et al ¹³	Grade 3/4 myelosuppression –Neutropenia (58 patients, 56%) –Thrombocytopenia (59 patients, 57%) –Leukopenia (51 patients, 49%) Grade 3/4 infection [†] –CMV reactivation [‡] (3 patients, IV cohort; 5 patients, SC cohort; 8% overall) –Non-CMV infections (30 patients, 29%) Injection-site reaction (1 patient)

*Phase III study of alemtuzumab vs chlorambucil.

[†]In the CLL2H study, one-third of patients were at high risk of infections due to the presence of grade 3/4 infections in the 6 months prior to study enrollment.

[‡]All CMV episodes were successfully managed with treatment.

CMV=cytomegalovirus; IV=intravenous; SC=subcutaneous.

difficulty with the ability to interpret and compare study results with other combination treatment regimens. Nevertheless, alemtuzumab-based and fludarabine-based regimens have shown significant activity in both first-line and relapsed or refractory CLL. Across all studies, myelosuppression, infectious events, and cytomegalovirus (CMV) reactivation have constituted the majority of grade 3/4 adverse events.

Recently, 2 multicenter, phase III, randomized, controlled studies compared first-line FCCam with fludarabine, cyclophosphamide, and rituximab (FCR)²⁹ or fludarabine and cyclophosphamide.³⁰ Dosing and administration for the studies were similar (oral fludarabine 40 mg/m² and cyclophosphamide 250 mg/m²), although there were variations in the initial dose escalation for alemtuzumab. In the first study, the French Cooperative Group on CLL and Waldenström's macroglobulinemia (FCGCLL/WM) and the Groupe Ouest-Est d'Etudes Des Leucémies Aigües et Autres Maladies du Sang (GOELAMS) examined FCCam (alemtuzumab 30 mg SC, days 1–3) versus FCR (rituximab 375 mg/m², day 0 of cycle 1, then 500 mg/m², day 1 of subsequent cycles) in treatment-naïve patients (<65 years) who had good performance status and no 17p deletions.²⁹ Following randomization of 165 patients, this trial was terminated prematurely because of excess mortality in the FCCam treatment arm. Preliminary study results were reported at ASH in 2009 for the first 100 patients. Three-quarters of

all patients completed 6 cycles of therapy. Interim data suggest that FCR treatment showed enhanced response compared with FCCam (ORR: 96% vs 85%; *P*=.086); the data remain to be finalized. Grade 3/4 neutropenia was a main cause of premature discontinuation; grade 4 neutropenia progressively increased from cycle 1 (28%) through cycle 6 (46%) in the FCCam treatment arm. In addition to elevated serious adverse events in the FCCam arm, 7 patients died of malignant transformation, infection-related events, and heart failure while experiencing neutropenia. These adverse events have triggered serious safety concerns with regard to the use of FCCam as first-line therapy.

In the second phase III, multicenter study, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON68) compared FCCam with fludarabine and cyclophosphamide in high-risk adult patients of any CLL stage.³⁰ Fludarabine and cyclophosphamide administration was similar to that in the FCGCLL/GOELAMS study; however, alemtuzumab was given at 30 mg SC on days -1, 0, and 1 of cycle 1, and day 1 of cycles 2–6. Following cycle 1, there was a two-thirds reduction in cumulative alemtuzumab concentration compared with the FCGCLL/WM/GOELAMS study. Safety data presented to date in a preliminary study report suggest an increased incidence of opportunistic infections (but not other types of infections) in the FCCam treatment arm.³¹

Table 3. Clinical Studies of Chemoimmunotherapy Combinations Including Alemtuzumab

	Route	Dosing Schema	No. of Patients	% ORR (% CR)	Toxicity
FluCam: Second-line or later					
Kennedy et al, 2002 ⁶	IV IV	Fludarabine 25 mg/m ² days 1–3 Alemtuzumab 30 mg TIW every 28 days to maximal response	6	83 (17)	Pseudomonas bronchopneumonia (1 patient) No CMV reactivation or treatment interruption
Phase II Elter et al, 2005 ⁵	IV IV	Fludarabine 30 mg/m ² days 1–3 Alemtuzumab 30 mg TIW days 1–3 × ≤6 cycles, every 28 days	36	83 (30)	Grade 3/4 myelosuppression –Leukopenia (44%) –Thrombocytopenia (30%) –Neutropenia (26%) Grade 3 CMV reactivation (2 patients) Grade 4 infection (3 patients) Opportunistic pneumonia (2 PD patients)
Flowers et al, 2007 ²²	IV SC	Fludarabine 25 mg/m ² days 1–5 Alemtuzumab 30 mg days 1–5 × ≤4 cycles, every 28 days	28	64 (21)	NR
CAM314: FluCam vs F Engert et al, 2009 ²³	IV IV	Fludarabine 30 mg/m ² days 1–3 Alemtuzumab 30 mg TIW days 1–3 vs	168	85 (30)	Grade 3/4 myelosuppression Symptomatic CMV reactivation (1% SAE in FluCam arm)
	IV	Fludarabine 25 mg/m ² days 1–5 × ≤6 cycles, every 28 days	167	68 (16)	Slightly elevated neutropenia and infection rate in FluCam arm
FCCam: Second-line or later					
Montillo et al, 2007 ²⁴	PO PO SC	Fludarabine 40 mg/m ² Cyclophosphamide 250 mg/m ² Alemtuzumab 10 mg SC On days 1–3 every 28 days × 6 cycles	19	79 (37)	Grade 3/4 neutropenia (43%) Grade 3/4 thrombocytopenia (8%) Major infections (2 <i>M. tuberculosis</i> , 1 <i>Nocardia</i> , 1 <i>E. coli</i>) CMV reactivation (6 patients)
CLL2L study Elter et al, 2009 ²⁶	IV IV SC	Fludarabine 25 mg/m ² Cyclophosphamide 200 mg/m ² Alemtuzumab 30 mg On days 1–3 every 28 days	52	68 (22)	5 fatal treatment-related events Grade 3/4 thrombocytopenia and neutropenia CMV reactivation (5 patients) Herpes zoster (1 patient) AIHA (1 patient) Fever of unknown origin (12 patients)
FCCam: First-line					
Phase III multicenter FCCam vs FCR Lepretre et al, 2009 ²⁹	PO PO SC	FCCam Fludarabine 40 mg/m ² Cyclophosphamide 250 mg/m ² Alemtuzumab 30 mg SC days 1–3 vs	165	85 (58)*	Grade 3/4 neutropenia Premature study discontinuation due to 7 deaths from malignant transformation, infection-related events, and heart failure while experiencing neutropenia in the FCCam arm
	IV	FCR (identical FC) Rituximab 375 mg/m ² day 0 cycle 1; 500 mg/m ² day 1 of subsequent cycles		96 (78)	
Phase III multicenter FCCam vs FC Geisler et al, 2010 ³⁰	PO PO SC	Fludarabine 40 mg/m ² Cyclophosphamide 250 mg/m ² with/without Alemtuzumab 30 mg on days -1, 0, and 1 of cycle 1; day 1 of cycles 2–6	Not yet reported	Not yet reported	Ongoing study

(Table continues on following page)

Table 3. (Continued) Clinical Studies of Chemoimmunotherapy Combinations Including Alemtuzumab

	Route	Dosing Schema	No. of Patients	% ORR (% CR)	Toxicity
CFAR					
Relapsed/ refractory Wierda et al, 2006 ²⁷	IV IV IV IV	Cyclophosphamide 200 mg/m ² days 3–5 Fludarabine 20 mg/m ² days 3–5 Alemtuzumab 30 mg days 1, 3, 5 Rituximab 375–500 mg/m ² day 2 every 28 days × 6 cycles	74	65 (24) 44 in patients with del(17p)	Grade 3 (20% courses) and 4 (39% courses) neutropenia Grade 3 (17%) and 4 (15%) thrombocytopenia CMV reactivation (12 patients)
First-line, high-risk Wierda et al, 2007 ²⁸	IV IV IV IV	Cyclophosphamide 200 mg/m ² days 3–5 Fludarabine 20 mg/m ² days 3–5 Alemtuzumab 30 mg days 1, 3, 5 Rituximab 375–500 mg/m ² day 2 every 28 days × 6 cycles	21	95 (71)	Grade 3/4 neutropenia and thrombocytopenia (27% and 7% of courses) Major and minor infections (2% and 8% of courses) Fever of unknown origin in 34% of courses CMV reactivation in patients receiving valacyclovir; none in patients receiving valganciclovir

*Interim data. ORR, $P=.086$; CR, $P=.072$.

AIHA=autoimmune hemolytic anemia; CFAR=cyclophosphamide, fludarabine, alemtuzumab, and rituximab; CMV=cytomegalovirus; CR=complete response; FCCam=fludarabine, cyclophosphamide, and alemtuzumab; FluCam=alemtuzumab plus fludarabine; FC=fludarabine and cyclophosphamide; FCR=fludarabine, cyclophosphamide, and rituximab; IV=intravenous; NR=not reported; ORR=overall response rate; PD=progressive disease; PO=oral; SAE=serious adverse event; SC=subcutaneous; TIW=3 times per week.

Studies of Nonchemotherapy Combination Regimens With Alemtuzumab

Immunotherapy combinations of alemtuzumab with the anti-CD20 antibody rituximab have been investigated to provide a dual-targeted approach in CLL patients and to minimize adverse events derived from chemotherapy-containing regimens. As detailed in Table 4, a number of studies with the combination of alemtuzumab and rituximab have been performed in relapsed or refractory patients,³²⁻³⁴ as well as in the first-line setting.^{35,36} Again, variations in the dosing regimens for alemtuzumab make the studies difficult to compare with one another. Dosing regimens for alemtuzumab are modified from the standard dosing regimen when used in an immunotherapy combination. In the relapsed/refractory setting, the combination regimen shows potentially improved response rates compared with single-agent, standard-dose alemtuzumab.

Studies of Consolidation With Alemtuzumab

Consideration of alemtuzumab as a consolidation treatment for CLL stems from alemtuzumab's significant clearing of minimal residual disease. In the initial investigation of standard-dose alemtuzumab as consolidation therapy following initial chemotherapy with fludarabine alone or in combination with cyclophosphamide, 7 of 11

patients withdrew from the study due to severe infection.³⁷ Although alemtuzumab consolidation was unfavorable from a safety perspective, it improved patient response to induction therapy, prolonged survival, and achieved minimal residual disease negativity. Long-term follow-up of patients receiving alemtuzumab consolidation continued to show significantly prolonged PFS at a median of 48 months, compared with patients who received no further treatment after induction chemotherapy.³⁸ Montillo and colleagues demonstrated an improvement in the quality of response following fludarabine-based induction with low-dose alemtuzumab (10 mg SC 3 times per week, ≤ 6 wk) consolidation, including an increase in CR rates from 35% to 79%, respectively.³⁹ Over half of the CR patients (56%) achieved minimal residual disease negativity. Adverse events were anticipated (injection-site reactions and fever), and episodes of CMV reactivation were successfully managed with oral ganciclovir. In 92% of patients, peripheral blood stem cell collection was successful, enabling 18 of 24 patients to go on to autologous stem cell transplantation. In the Cancer and Leukemia Group B (CALGB) study 19901, patients who responded to or achieved stable disease with initial fludarabine (25 mg/m² for 5 days, 4 cycles followed by observation) received alemtuzumab 30 mg 3 times per week IV or SC for 6 weeks.⁴⁰ Both IV and SC alemtuzumab consolidation led to improved ORRs and CR rates, with decreased systemic adverse events

Table 4. Clinical Studies of Immunotherapy Combinations of Alemtuzumab and Rituximab

	Route	Dosing Schema	No. of Patients	% ORR (% CR)	Toxicity
Relapsed/Refractory					
Faderl et al, 2003 ³²	IV IV	Rituximab 375 mg/m ² weeks 1–4 Alemtuzumab dose escalation week 1, 30 mg BIW weeks 2–4	32	63 (6)	Grade 1/2 infusion-related reactions Infections (52%) CMV reactivation (27%) and symptoms (17%) Fever of unknown origin (13%)
Faderl et al, 2005 ³³	IV CIV	Rituximab 375 mg/m ² week 1; 1,500 mg/m ² weeks 2–4 Alemtuzumab 15 mg/d CIV days 2–7, 30 mg SC week 2–4	20	55 (30)	Grade 1/2 infusion-related reactions CIV tolerated better than bolus infusion Infections (50%); CMV reactivation (21%)
Nabhan et al, 2004 ³⁴	IV IV	Rituximab 375 mg/m ² weeks 1, 3–5 Alemtuzumab 3/10/30 mg TIW weeks 2–5	11	9 (0)	Majority infusion-related No CMV reactivation/infection
First-line					
Frankfurt et al, 2007 ³⁵	IV SC	Rituximab 375 mg/m ² every other week from week 3 Alemtuzumab dose escalation; then 30 mg weeks 1–17	11	100 (72)	CMV reactivation (4 patients); no organ disease No serious infection Grade 3/4 lymphopenia (all patients) and neutropenia (5 patients) No autoimmune disease/Richter's transformation
Zent et al, 2008 ³⁶	IV SC	Rituximab 375 mg/m ² for 4 weeks Alemtuzumab dose escalation days 1–3; then 30 mg TIW for 4 weeks	30	90 (37)	Grade 3/4 neutropenia (5 patients) No grade 3/4 anemia or thrombocytopenia CMV reactivation (3 patients)

BIW=2 times per week; CIV=continuous infusion; CMV=cytomegalovirus; CR=complete response; IV=intravenous; NR=not reported; ORR=overall response rate; PO=oral; SAE=serious adverse event; SC=subcutaneous; TIW=3 times per week.

following SC alemtuzumab. CMV infections occurred in 9 of 59 patients (15%), resulting in 1 death. Recommendations for future consolidation studies include frequent monitoring for CMV reactivation, with possible preemptive or prophylaxis treatment for CMV,⁴⁰ as well as the use of alemtuzumab consolidation only in patients with remaining tumor burden after induction and at least 3 months following induction.³⁹ Overall, these studies showed favorable responses and achievement of minimal residual disease negativity following alemtuzumab consolidation with low-dose alemtuzumab or an abbreviated course of standard-dose alemtuzumab. However, preliminary results of a CALGB study reported severe and life-threatening toxicity in patients treated with alemtuzumab consolidation following induction with fludarabine and rituximab (FR).⁴¹ In this trial, alemtuzumab-related infectious deaths in patients in CR after FR led to a protocol

amendment allowing only patients in partial response after FR induction to receive treatment with alemtuzumab. Final study results suggest that alemtuzumab consolidation after FR, although limited by toxicity, improved CR and minimal residual disease negative rates; long-term follow-up remains to determine the potential impact on survival.⁴² Clinical trials are ongoing to determine optimal dose, route of administration (IV vs SC), and schedule for alemtuzumab in consolidation.

Safety: Alemtuzumab Administration, Pharmacokinetics, and Management

The inherently complex nature of antibody therapy and inpatient variability in pharmacokinetics for alemtuzumab lends some difficulty in establishing a pharmacokinetic profile for alemtuzumab-treated patients.⁴³

However, because there appears to be major variation in the pharmacokinetics for IV versus SC alemtuzumab, the clear advantage in the safety profile and convenience favors the SC over IV route of administration with the 3 times weekly administration scheme.⁴⁴ For all combinations with a 4-week interval, we can presume from the results of pharmacokinetic studies conducted using the 3 times weekly administration that problems may result from using it as an SC administration instead of an IV administration, as sufficient plasma levels are not reached. In the majority of patients, initial infusion-related reactions (eg, fever, rash, rigors, nausea) in the first week of treatment are common and generally mild (grade 1/2). Prophylactic use of antihistamines and acetaminophen reduce these initial reactions. Hematologic adverse events are most common between weeks 2–8 of alemtuzumab treatment (thrombocytopenia weeks 2–4; neutropenia weeks 4–8), are reversible, and may be managed with growth factor support or transfusions. The inherent immunosuppressive nature of alemtuzumab leads to an increased susceptibility to infections, particularly opportunistic infections. The incorporation of antibacterial and antiviral prophylaxis significantly reduces the incidence of these infections.¹¹ CMV reactivation is well documented in alemtuzumab-containing regimens. Upfront prophylaxis and frequent monitoring are recommended to aggressively manage any symptomatic CMV reactivations.⁴⁵

Recently updated management guidelines for the use of single-agent alemtuzumab provide recommendations for adequate management of adverse events.⁸ A panel of practicing CLL experts who met at an advisory board meeting in Madrid, Spain reached a consensus on the following points⁸:

- Single-agent alemtuzumab may be a safe first-line treatment for CLL.
- Suitable patient populations for receiving alemtuzumab (first-line or following relapse or refractoriness) include those who are elderly, have 17p deletions, demonstrate pancytopenia due to infiltrated bone marrow, and have refractory autoimmune cytopenia.
- The standard dose should be 30 mg/day given 3 times per week, with a duration of 12 or more weeks; bone marrow evaluation of response is recommended at week 12.
- Weekly monitoring for CMV reactivation is recommended; treatment is held if the patient is symptomatic.
- SC delivery is recommended to provide simplified and safer administration and to improve safety with efficacy equivalent to that of IV delivery.

Although these guidelines are effective for the use of single-agent alemtuzumab, incorporation of alemtuzumab into combination regimens or in consolidation is

less standardized and requires further study in controlled clinical trials.

Conclusion

Continued clinical evaluation of alemtuzumab in CLL has provided a range of findings over the past 2 decades. As a monotherapy, standard-dose alemtuzumab demonstrates reproducible results in relapsed or refractory therapy, as well as first-line therapy. Adverse events are generally predictable and can be managed with prophylaxis and frequent monitoring to ensure that patients stay on therapy for optimal response. Initial therapy with alemtuzumab has demonstrated improved efficacy over chlorambucil, as well as prolonged duration of response, particularly in patients achieving an initial CR and minimal residual disease negativity. Combination regimens incorporating alemtuzumab show promising effects for overall response and response duration, but patient selection according to the mentioned guidelines is mandatory. In consolidation, low-dose alemtuzumab or an abbreviated course of standard-dose alemtuzumab provides a durable patient response by targeting minimal residual disease following induction therapy.

SC administration of alemtuzumab provides an improvement in infusion-related adverse events and enhanced convenience for a more cost-effective therapy. Although a direct pharmacokinetic comparison of the same schedule using 2 different routes of administration remains to be examined in clinical trials, it is suggested that if alemtuzumab is used outside the approved thrice-weekly schedule, it should still be given intravenously.

The overarching question for combination treatment of patients with CLL remains: What are the ideal dose and duration of alemtuzumab treatment so that its benefit-to-risk ratio provides beneficial clinical outcomes while minimizing significant adverse consequences? Although continued study is warranted to ensure standardization of alemtuzumab therapy in the combination and consolidation settings, the following recommendations are provided based on current studies of alemtuzumab monotherapy, in combination, or consolidation:

- Standard-dose alemtuzumab is safe when used early (ie, first-line or first relapse).
- Existing guidelines for use of alemtuzumab should be followed.
- For standard alemtuzumab dosing, SC administration is recommended to reduce adverse events.
- The IV route of administration may be considered preferable when it is not possible to obtain information regarding the patient's pharmacokinetic profile or to establish the potential synergy of alemtuzumab when given in combination with other drugs.

- Weekly monitoring for CMV reactivation is important; preemptive or prophylaxis treatment for CMV symptoms may be warranted.

Acknowledgment

The development of this article was supported by Genzyme Corporation. The authors would like to thank Julie Kern, PhD, for editorial support.

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