Alemtuzumab use in relapsed and refractory chronic lymphocytic leukemia: a history and discussion of future rational use

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Abstract: In this review, we outline the clinical experience with single-agent alemtuzumab as a treatment for relapsed and refractory chronic lymphocytic leukemia (CLL) in both prospective and retrospective trials and describe the multiagent use of the drug with the goal of updating clinicians on recent developments and possible future rational combinations. Alemtuzumab, an antibody targeting the lymphocyte-specific surface marker CD52, is an approved agent for the treatment of CLL. Despite its demonstrated efficacy, likely secondary to concerns regarding infectious complications, it is most commonly used in the relapsed and refractory setting. Given alemtuzumab's unique mechanism of action it has been demonstrated to have activity in disease that is refractory to both alkylating agents and purine analogs. Furthermore, it has activity in TP53-mutated disease, which has the worst prognosis of any subset of CLL. Alemtuzumab has greater efficacy on circulating disease relative to nodal disease. Rational combinations are attempting to use these attributes to increase response rates in patients with relapsed and refractory disease.

Keywords: agammaglobulinaemia tyrosine kinase, alemtuzumab, B cell, CD52 antigen, chronic, leukemia, lymphocytic, phosphatidylinositol 3 kinase, recurrence

Background

Chronic lymphocytic leukemia (CLL) is the most common indolent leukemia, with an estimated 14,570 new cases in the United States in the year 2012 alone [Siegel *et al.* 2011]. Because the natural history of the disease can span decades, and because there are many efficacious but noncurative therapies available, most patients will experience a relapse after first-line treatment. A large minority of patients will not achieve complete remission with first-line treatment or their disease will progress within 6 months of antileukemic treatment, and as such, are considered to be refractory, as per the 2008 National Cancer Institute Working Group (NCI-WG) guidelines [Hallek *et al.* 2008]. The treatment options for relapsed or refractory CLL have expanded over time, to include targeted therapies such as alemtuzumab (Campath, Novartis, Basel, Switzerland), a partially humanized rat monoclonal antibody targeting CD52, a surface marker found on healthy and malignant lymphocytes. The purpose of this article is to review the use of alemtuzumab in the treatment of relapsed or refractory CLL

and its future potential applications, with a focus on rational combinations to capitalize on alemtuzumab's efficacy in relapsed and refractory disease and treatment effect on circulating tumor.

History and mechanism of action of alemtuzumab

The precursor to alemtuzumab was derived from rat antibodies directed against proteins expressed on human lymphocytes. This monoclonal antibody, called CAMPATH-1 (University of Cambridge, Pathology Department), was created as a means of depleting mature T lymphocytes from marrow grafts, in an effort to reduce the incidence of graft *versus* host disease [Hale *et al.* 1983a]. In the initial published report, an *in vivo* experiment of two patients, one with non-Hodgkin lymphoma (NHL) and one with CLL, was briefly reported as having no adverse effect [Hale *et al.* 1983b, 1988]. The earliest trials involved an immunoglobulin (Ig)-M variant (CAMPATH-1M) and an IgG2b variant (CAMPATH-1G). However, concerns about anaphylaxis led to humanization of

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Table 1. Alemtuzumab single-agent trials in relapsed/refractory chronic lymphocytic leukemia (CLL).

Trial	No. enrolled	Median prior lines (range)	ORR, % (CR, %)	Median OS, months	Median PFS, months	Patient characteristics
Osterborg <i>et al.</i> [1997]	29	nr	41 [3]	nr	12*	r/r
Keating [2002] (CAM-211)	93	3 [2–4 [§]]	33 [2]	16	4.7	Fludarabine r/r
Rai <i>et al.</i> [2002]	24 (23 CLL, 1 T-PLL)	3 [1–8]	33 [0]	35.8	19.6	Fludarabine refractory
Ferrajoli <i>et al.</i> [2003]	78 (42 CLL, 18 T-PLL, 18 others)	3 [1–9] [§]	31 [5]*	12 [†]	Nr	Relapsed or no established frontline therapy
Lozanski <i>et al.</i> [2004]	36	3 [1–12]	31 [6]	nr	10 [§]	81% fludarabine r/r
Rawstron <i>et al.</i> [2004]	43	3 [1–7]	37 [21]	nr	Nr	r/r to purine analogs
Moreton <i>et al.</i> [2005]	91 [¶]	3 [1–8]	54 [35]	nr but MRD better	Nr	r/r
Ionita <i>et al.</i> [2009]	27	3 [1–6]	33 [7.4]	19.1	7.7	Fludarabine refractory
Total number treated	421					

Only trials with enrollment of 20 or more patients are shown. Unless otherwise noted, all patients have CLL.
 *Response duration.
 §Patients with CLL only.
 †All patients.
 §Responders.
 ¶Seven received subcutaneous treatment.
 CR, complete response; MRD, minimal residual disease; nr, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed/refractory; T-PLL, T-cell prolymphocytic leukemia.

the antibody, now called CAMPATH-1H and commercially named alemtuzumab [Riechmann *et al.* 1988]. The target of the antibody was elucidated in 1991 as the CAMPATH-1 antigen, CD52 [Xia *et al.* 1991]. CD52 was eventually determined to be a glycosylphosphatidylinositol-anchored antigen which is expressed on mature lymphocytes [Xia *et al.* 1993], including malignant lymphocytes, and to a lesser degree on monocytes, dendritic cells, and the male genital tract [Buggins *et al.* 2002]. Alemtuzumab causes cell death primarily through complement-mediated cell lysis, antibody-dependent cellular toxicity, and possibly induction of apoptosis [Xia *et al.* 1993; Golay *et al.* 2004; Nuckel *et al.* 2005; Mone *et al.* 2006].

Evidence of efficacy of single-agent alemtuzumab in relapsed/refractory chronic lymphocytic leukemia

Given the high expression of CD52 on lymphocytes, the early testing of alemtuzumab was

focused exclusively on patients with lymphoproliferative disease. Early investigations in patients with NHL suggested that the agent was more effective on tumor cells in the blood and bone marrow compartments, as opposed to the lymph nodes [Dyer *et al.* 1990; Lim *et al.* 1993]. Owing to this finding, the focus of evaluation turned towards CLL. The standard of care for relapsed or refractory CLL, in the 1990s, was the use of purine analogues (such as fludarabine) and/or allogeneic stem cell transplant [Cheson, 1991; Byrd *et al.* 2000; Montserrat *et al.* 2006]. Two pilot phase II studies and one larger international phase II study of single-agent intravenous alemtuzumab were conducted in the mid 1990s (Table 1). In one of the pilots, Osterborg and colleagues, in Europe, evaluated the overall response rate (ORR), as defined by the 1988 NCI-WG guidelines [Cheson *et al.* 1988], in 29 patients who had been previously treated (not necessarily with purine analogs, including fludarabine). A total of 38% of patients achieved a partial response (PR),

and one achieved a complete response (CR) [Osterborg *et al.* 1997]. In the second pilot, Rai and colleagues, in the USA, evaluated 24 heavily pretreated patients who had progressed after fludarabine-containing therapy. A total of 33% of these patients achieved a PR, with a median duration of response of 15.4 months [Rai *et al.* 2002]. The largest trial, CAM-211, was conducted at 21 different centers in Europe and the USA, and evaluated 93 heavily pretreated patients, who had relapsed after fludarabine, for ORR [Keating, 2002]. A total of 31 of these patients experienced a response (ORR 33%), including two CRs; 50 patients (54%) had stable disease (SD).

The three single-arm phase II studies (CAM-211 and those by Osterborg and colleagues and Rai and colleagues) [Osterborg *et al.* 1997; Rai *et al.* 2002] led to accelerated Food and Drug Administration (FDA) approval, which was granted on 7 May 2001. This approval was for 'patients who have been treated with alkylating agents and who have failed fludarabine therapy'. As per the FDA regulation, all accelerated approvals require a subsequent randomized trial to demonstrate efficacy to convert to a full approval. This requirement was met with the CAM-307 trial, which randomized untreated patients with CLL to single-agent chlorambucil *versus* single-agent alemtuzumab [Hillmen *et al.* 2007]. This trial found a statistically significant improvement in progression free survival (PFS), with a median PFS of 14.6 months in the alemtuzumab group *versus* 11.7 months in the chlorambucil group ($p = 0.0001$). This led to an expanded label indication to include previously untreated patients with B-CLL, granted on 19 September 2007.

Subsequent to the initial seminal phase II trials, we identified 12 further published trials examining the efficacy of single-agent intravenous alemtuzumab in the relapsed setting [Ferrajoli *et al.* 2003; Lozanski *et al.* 2004; Rawstron *et al.* 2004; Rieger *et al.* 2004; Thieblemont *et al.* 2004; Laurenti *et al.* 2005; Lin *et al.* 2005; Moreton *et al.* 2005; Majolino *et al.* 2006; Ionita *et al.* 2009; Kataeva *et al.* 2009; Zagorskina *et al.* 2011]. Five of these trials had at least 20 patients enrolled (Table 1). Similar to the initial trials, these five all included heavily pretreated patients, with a median of three prior lines of treatment (range 1–12). ORR, primarily based upon the updated 1996 NCI-WG guidelines [Cheson *et al.* 1996], range from 31% to 54%, with CR rates of 5–35%. Median PFS and overall survival (OS), when

reported, range from 7.7 to 10 months and 12 to 19.1 months respectively. Minimal residual disease was assessed in one of these trials [Rawstron *et al.* 2004], and patients who had persistent flow cytometric evidence of circulating CLL cells 4 weeks into treatment were unlikely to experience a significant response [Rawstron *et al.* 2004].

Immediate toxicities and the alternative of subcutaneous administration

In the initial trials, prior to humanization, CAMPATH-1M and CAMPATH-1G caused fevers and rigors in most patients, along with transient transaminitis. The subsequent phase I trials with intravenous alemtuzumab also observed high rates of immediate transfusion reactions, including fevers, rigors, rash, and nausea. Although for the most part these reactions were observed to be mild and were somewhat ameliorated by the prior administration of paracetamol or acetaminophen and diphenhydramine, the general practice moved towards a dose-escalation method of administration. The most common dose-escalation method was to start administration with a dose of 3 or 10 mg, and increase to a final target dose of 30 mg thrice weekly (e.g. Osterborg and colleagues, Rai and colleagues and CAM-211 all used this general approach) [Osterborg *et al.* 1997; Rai *et al.* 2002]. The most recent FDA package insert (September 2007) recommends a dose of 3 mg daily until infusion reactions are up to grade 2, followed by 10 mg daily until infusion reactions are up to grade 2, followed by 30 mg three times a week for up to 12 weeks.

Acute or subacute tumor lysis syndrome (TLS) is a significant concern with conventional cytotoxic therapies as well as some targeted therapies such as rituximab, especially when the burden of CLL is high [Cheson, 2009]. Despite this general concern, acute and/or subacute TLS has not been observed commonly with alemtuzumab. For instance, there were no reports of TLS as a gradable toxicity in the CAM-307 trial [Hillmen *et al.* 2007].

In a quest to evaluate a less toxic administration route, Hale and colleagues demonstrated that blood concentrations of alemtuzumab delivered via the subcutaneous route were comparable to those achieved by the intravenous route, although a higher cumulative dose was required to achieve a similar concentration [Hale *et al.* 2004]. Efficacy

Table 2. Alemtuzumab single-agent trials using the subcutaneous route.

Trial	No. enrolled	Median prior lines (range)	ORR, % (CR, %)	Median OS, months	Median PFS, months	Patient characteristics
Cortelezzi <i>et al.</i> [2009]	49	2 [1–5]	53 (27)	30	8	r/r
Karlsson <i>et al.</i> [2009]	20	2 [1–4 [§]]	75 (15)	Not reached	20	r/r
Stilgenbauer <i>et al.</i> [2009] (CLL2H)	109	3 [1–10]	32 (4)	19.1	7.7	Fludarabine refractory
Varghese <i>et al.</i> [2010] (UKCLL02)	53*	Nr	45 (15)	20.2	13	Fludarabine r/r
Bezares <i>et al.</i> [2011]	62	1.6 [1–4]	95 (51)	~30	~24 [§]	Fludarabine r/r
Gritti <i>et al.</i> [2012]	39	3 [1–6]	44 (8)	29.1	10.3	Fludarabine r/r
Total number Treated	332					
Only trials with enrollment of 20 or more patients are shown; all patients have chronic lymphocytic leukemia.						
*Seventeen patients re-exposed to fludarabine.						
§Event-free survival.						
CR, complete response; nr, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed/refractory.						

was not evaluated in this study, although it was noted that 2 of 32 patients (6%) who received subcutaneous treatment developed anti-alemtuzumab antibodies. Prior to this investigation, several pilot studies had explored the clinical use of subcutaneous alemtuzumab and reported that immediate flu-like toxicities were less severe in these groups; additionally, the clinical observation of several sustained remissions suggested that the subcutaneous route could still be efficacious [Osterborg *et al.* 1996; Bowen *et al.* 1997]. These early encouraging signals led to a larger trial in untreated patients, with 26 PRs and 7 CRs observed in 41 patients (ORR = 80.5%) [Lundin *et al.* 2002]. Subsequently, several phase II trials in the relapsed/refractory setting have been performed; those enrolling at least 20 patients are shown in Table 2 [Cortelezzi *et al.* 2005, 2009; Ferrajoli *et al.* 2008; Karlsson *et al.* 2009; Stilgenbauer *et al.* 2009; Varghese *et al.* 2010; Bezares *et al.* 2011; Kaufman *et al.* 2011; Gritti *et al.* 2012]. The largest of these, the German CLL2H trial, enrolled 109 fludarabine refractory patients and found a 32% ORR, similar to the historic intravenous trials [Stilgenbauer *et al.* 2009]. Several Italian studies by Cortelezzi and colleagues have found that a low-dose subcutaneous treatment strategy can lead to response rates

in the 44–53% range, with minimal toxicity. Bezares and colleagues demonstrated a very high response rate (95%, including 51% CR) using an extended course of subcutaneous alemtuzumab, up to 52 weeks [Bezares *et al.* 2011]. A trial comparing subcutaneous alemtuzumab with standard dose escalation *versus* starting at full dose (30 mg subcutaneously three times a week) has enrolled 85 patients; no results have been announced as of yet [ClinicalTrials.gov identifier: NCT00328198].

Despite the encouraging findings, to date, the official FDA indication is for the intravenous route only; therefore, subcutaneous administration is considered to be off label. This may be due to the fact that, in contrast to subcutaneous administration of bortezomib for multiple myeloma [Moreau *et al.* 2011], no formal noninferiority study has been undertaken. However, many practicing oncologists have shifted to a subcutaneous strategy in an effort to mitigate infusion-related toxicities.

Delayed toxicities and the role of infection prophylaxis

As the clinical experience with alemtuzumab has accumulated, serious long-term adverse

complications have become recognized. These complications are largely infectious in nature, and are likely primarily due to the CD4 T-lymphocyte depletion that occurs as a bystander casualty of alemtuzumab. The median T-cell nadir occurs 17 days after treatment with alemtuzumab [Moreton *et al.* 2005] and patients continue to be at increased infectious risk for at least 6 months following treatment. A small series demonstrated that T-cell repertoire, as well as magnitude, is perturbed for many months following alemtuzumab treatment [Rezvan *et al.* 2006].

As a result of increased recognition of the dangers of delayed infectious complications, it is recommended to place patients on a prophylactic regimen of an agent directed against herpes simplex virus (e.g. acyclovir, famciclovir) and an agent directed against *Pneumocystis jirovecii* (PCP, e.g. trimethoprim/ sulfamethoxazole) during the course of treatment and for at least 6 months after completion of treatment [Osterborg *et al.* 2009]. Notably, Lundin and colleagues demonstrated that only 50% of patients treated with subcutaneous alemtuzumab had recovered a CD4 T-lymphocyte count to over 100 cells/ μ l at 4 months post treatment [Lundin *et al.* 2004]. Some practitioners continue pneumocystis prophylaxis until the CD4 T-lymphocyte count recovers to above 200 cells/ μ l.

Another major concern which emerged early in the experience of alemtuzumab is cytomegalovirus (CMV) reactivation. For example, the CAM-307 trial had a 52% rate of CMV reactivation in the alemtuzumab arm, with 31% of these reactivations considered symptomatic. Owing to the toxicity of anti-CMV therapies (notably, bone marrow suppression), it is not routine to use a prophylactic strategy, although there are limited data on valganciclovir prophylaxis [O'Brien *et al.* 2008]. Instead, it is recommended to check polymerase chain reaction for CMV viremia weekly during treatment, and to institute therapy if a viral load becomes detectable [O'Brien *et al.* 2006; Osterborg *et al.* 2009].

As experience with alemtuzumab increased, it was also recognized that neutropenia is a significant side effect of treatment, and trial patients were treated with granulocyte stimulatory agents to prevent neutropenia and infections [Cortelezzi *et al.* 2009; Karlsson *et al.* 2009; Stilgenbauer *et al.* 2009; Bezares *et al.* 2011]. Granulocyte stimulatory agents are recommended under

current treatment guidelines to prevent neutropenia [Osterborg *et al.* 2009].

Combination strategies and the search for synergy

As with other targeted drugs and conventional chemotherapeutics, the search for synergy has led to explorations of combination strategies using alemtuzumab. This has especially been driven by the early recognition that alemtuzumab is of limited efficacy in bulky lymphadenopathy [Lundin *et al.* 1998]. As shown in Table 3, most of the larger trials have evaluated the combination of alemtuzumab with rituximab or with fludarabine. We identified 14 nonrandomized two-agent trials [Kennedy, 2002; Faderl *et al.* 2003, 2010; Nabhan *et al.* 2004; Elter *et al.* 2005; Pettitt *et al.* 2006, 2012; Flowers *et al.* 2007; Egle *et al.* 2009, 2010; Brown *et al.* 2010; Stilgenbauer *et al.* 2010; Tedeschi *et al.* 2011; Pospisilova *et al.* 2012], three nonrandomized three-agent trials [Montillo *et al.* 2011; Zent *et al.* 2011; Elter *et al.* 2012], one nonrandomized four-agent trial [Badoux *et al.* 2011], and two randomized trials [Gribben *et al.* 2005; Elter *et al.* 2011]. In addition, UKCLL02 (Table 2) re-exposed 17 fludarabine-refractory patients (32% of the cohort) to fludarabine in combination with alemtuzumab [Varghese *et al.* 2010]. Notably, although side effects in the combination trials to date have generally been tolerable, two recently published first-line trials evoke a cautionary note. One, a first-line trial of fludarabine and rituximab, followed by intravenous alemtuzumab, had very high rates of serious adverse events, including two fatalities attributable to alemtuzumab, out of 41 patients [Hainsworth *et al.* 2008]. More recently, a large randomized trial comparing fludarabine, cyclophosphamide, and alemtuzumab (FCA) to the standard first-line treatment, fludarabine, cyclophosphamide, and rituximab (FCR), was stopped early due to excess mortality in the FCA arm [Hallek, 2012; Lepretre *et al.* 2012].

As with the first-line trials, the phase II combination trials have included heavily pretreated patients, with a median of two to four prior lines of therapy (range 0–14). ORRs have been considerably higher than in the single-agent trials, 47–83%. Median OS is also encouraging, ranging from 11 to 47 months; median PFS ranges from 6 to 24.4 months. Although these numbers compare favorably with those attained in the single-agent trials, it should be noted that the combination

Table 3. Trials of combination regimens, primarily in relapsed/refractory chronic lymphocytic leukemia (CLL), with at least 20 patients enrolled.

Trial	Regimen (route)	No. enrolled	Median prior lines (range)	ORR, % [CR, %]	Median OS, months	Median PFS, months	Patient characteristics
Faderl <i>et al.</i> [2003]	A (IV) + R (IV)	48 (32 CLL, 9 CLL/PLL)	4 (1–9)	52 (8)	11	6	r/r
Elter <i>et al.</i> [2005]	A (IV) + F (nr)	36	2 (1–8)	83 (31)	35.6	13	r/r
Flowers <i>et al.</i> [2007]	A (SC) + F (IV)	28	3 (1–14)	64 (21)	nr	nr	r/r
Brown <i>et al.</i> [2010]	A (SC) + R (IV)	28	4 (1–11)	64 (14)	47	13	r/r
Faderl <i>et al.</i> [2010]	A (IV) → A (SC) + R (IV)	40	3 (1–8)	53 (18)	nr	6	r/r
Stilgenbauer <i>et al.</i> [2010] (CLL20)	A (SC) + Dex (PO) → A (SC) or allogeneic SCT (patient preference)	50	2 (1–5 17p-relapse, 1–6 F r/r)	47 (0) F r/r; 78 (0) 17p-relapse	nr	nr	Fludarabine r/r (N = 19); 17p- untreated (N = 22); 17p-relapsed (N = 9)
Badoux <i>et al.</i> [2011]	A (IV) + F (IV) + Cy (IV) + R (IV)	80	3 (1–14)	65 (29)	16.7	10.6	r/r
Elter <i>et al.</i> [2011]*	A (IV) + F (IV) <i>versus</i> F (IV)	335	nr	82 (13) <i>versus</i> 75 (4) (<i>p</i> = NS)	Not reached <i>versus</i> 52.9 (<i>p</i> = 0.02)	23.7 <i>versus</i> 16.5 (<i>p</i> = 0.0003)	r/r
Montillo <i>et al.</i> [2011]	A (SC) + F (PO) + Cy (PO)	43 [§]	2 (1–4)	67 (30)	33.6	24.4	r/r
Tedeschi <i>et al.</i> [2011]	A (SC) + B (IV)	29	2 (1–6)	61 (26)	nr	nr	r/r
Elter <i>et al.</i> [2012] (CLL2L)	A (SC) + F (IV) + Cy (IV)	61	1 (0–4)	56 (11)	45	17	r/r (N = 56); high risk untreated (N = 5)
Pettitt <i>et al.</i> [2012] (CLL206)	A (IV) → A (SC) + methylprednisolone (nr)	39	nr (1–4)	77 (14)	23 (all)	6.5 (r/r)	TP53 deleted (all); r/r (N = 22); untreated (N = 17)
Total number Treated		817					

Unless otherwise noted, all patients had CLL.
A, alemtuzumab; B, bendamustine; CR, complete response; Cy, cyclophosphamide; Dex, dexamethasone; F, fludarabine; IV, intravenous; nr, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLL, prolymphocytic leukemia; PO, oral; R, rituximab; r/r, relapsed/refractory; SC, subcutaneous.
*Phase III randomized trial.
[§]46% 17p- or 11q-.

trials have been conducted much more recently and thus may not be directly comparable to the single-agent trials. A very small trial randomized four patients to alemtuzumab plus fludarabine, *versus* eight randomized to rituximab and fludarabine; although the ORR was higher in the

alemtuzumab arm (75% *versus* 38%); the numbers are too small to draw any definite conclusions [Gribben *et al.* 2005]. Intriguingly, Brown and colleagues used a high-dose subcutaneous alemtuzumab design, with up to 90 mg administered once weekly, in combination with weekly

rituximab [Brown *et al.* 2010]. Although these patients were very heavily pretreated, with a median of four prior lines of therapy, the median OS of 47 months is the most encouraging of any nonrandomized alemtuzumab trial in the relapsed/refractory setting. The least invasive published trial, with subcutaneous alemtuzumab, oral cyclophosphamide, and oral fludarabine, had a good median PFS of 24.4 months and median OS of 33.6 months, despite a high prevalence of poor-risk cytogenetics [Montillo *et al.* 2011].

The most significant trial to be published regarding the use of alemtuzumab in the setting of relapsed CLL was a multicenter randomized phase III trial comparing the combination of fludarabine and alemtuzumab with fludarabine alone in 335 patients with relapsed CLL [Elter *et al.* 2011]. Median prior lines of therapy were not reported, but patients had received a range of one to four prior therapies, and 40% in each arm were considered refractory. Prior alemtuzumab or fludarabine was allowed, as long as the patient had achieved a response of SD or better, for at least 12 months. In contrast to the majority of single-arm studies that evaluated ORR as the primary endpoint, this trial was powered to detect a 50% difference in median PFS between the two groups. In fact, ORR was not significantly different between the groups, whereas median PFS was improved in the fludarabine plus alemtuzumab group [23.7 *versus* 16.5 months, hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.47–0.80, $p = 0.0003$]. In addition, median OS was improved in the two-agent group (not reached *versus* 52.9 months, HR 0.65, 95% CI 0.45–0.94, $p = 0.021$).

Retrospective analyses give further insight into toxicity and comparative effectiveness

Several groups have conducted retrospective analyses of alemtuzumab, as shown in Table 4. We identified six studies primarily focused on efficacy, which allows for several conclusions about comparative effectiveness [Osuji *et al.* 2005; Fiegl *et al.* 2006, 2010, 2011; Hui *et al.* 2008; Cortelezzi *et al.* 2012]. Similar to the clinical trial setting, the general usage of alemtuzumab appears to be limited to heavily pretreated patients, with a median range of two to four prior lines of therapy across the studies. One study only included patients who had previously been treated with alemtuzumab, and had encouraging PFS and OS results [Fiegl

et al. 2011]. The overall median OS in these studies range from 15.1 to 39 months, and the median PFS ranges from 4 to 19.4 months, with the majority less than 9 months.

An additional five studies were focused on safety, in particular infectious complications [Martin *et al.* 2006; Albo *et al.* 2007; Laros-Van Gorkom *et al.* 2007; Ursuleac *et al.* 2011; Vallejo *et al.* 2011]. These studies recapitulate the concern for CMV reactivation which was noted in the prospective clinical trials, with rates upwards of 39%. Vallejo and colleagues noted that the CMV reactivation rate was 75% in the subgroup of their series who had received a cumulative alemtuzumab dose of over 1000 mg. Overall infection rates varied across the series, with one study reporting that infection was the proximal cause of 26% of observed mortality [Martin *et al.* 2006].

Although the aggregate number of patients observed across these retrospective studies ($N = 659$) is not large, they do suggest that alemtuzumab can be effective in real-world settings, with a tolerable toxicity profile.

High-risk groups and future directions

Patients with tumor protein 53 (*TP53*) deletions have the worst prognosis of any CLL subgroup, with a median survival of 32 months from diagnosis [Dohner *et al.* 2000]. These patients are often refractory to initial therapy. In 2002, a patient with fludarabine refractory, *TP53*-deleted CLL was reported to have had a complete response to single-agent alemtuzumab, suggesting a *TP53*-independent mechanism for alemtuzumab [Stilgenbauer and Dohner, 2002]. The most recent evidence supporting this mechanism are the final results from the CLL206 trial, of alemtuzumab combined with high-dose steroids in patients with *TP53* deletion (22 previously treated and 17 untreated), who had a 77% ORR and a reasonable median OS of 23 months in the previously treated group [Pettitt *et al.* 2012]. Despite aggressive infectious prophylaxis, serious infections were seen in 51% of patients, but only in 29% of patients under 60 years of age. In younger patients, infectious complications compared favorably with traditional CLL induction regimens. New recommendations issued by the European Research Initiative on CLL now recommend the consideration of upfront alemtuzumab in patients with *TP53* deletion [Pospisilova *et al.* 2012].

Table 4. Published retrospective analyses of alemtuzumab usage in the clinic.

Trial	Years of analysis	Country (sites)	No. enrolled	Median prior lines (range)	Primary endpoint	ORR, % (CR, %)	Median OS, months	Median PFS, months	Notes
Osuji <i>et al.</i> [2005]	nr	UK (nr)	28	4 (1–11)	Efficacy	54 (18)	nr	4	
Fiegl <i>et al.</i> [2006]	2001–2006	Austria (25)	115	3 (1–11)	Efficacy	23 (5)	20.2	6.2	
Martin <i>et al.</i> [2006]	2001–2003	USA (1)	27 (21 CLL)	CLL: 3 (1–13)	Infection	nr	nr	nr	9 OI and 30 non-OI; 26% infectious mortality
Albo <i>et al.</i> [2007]	2001–2006	Spain (5)	24	3 (0–6)	Infection	nr	nr	nr	35 infectious episodes with 14% attributable mortality; 31% CMV-R
Laros-Van Gorkom <i>et al.</i> [2007]	2001–2005	Netherlands (15)	27	3 (0–8)	Complications	63 (15)	nr	8.3	12 infectious episode
Hui <i>et al.</i> [2008]	2002–2006	Canada (10)	42 (39 CLL)	CLL: 4 (1–8)	Efficacy and safety	50 (2)	15.1	5.4	60% infection rate
Fiegl <i>et al.</i> [2010]	2001–2007	Austria (17); Italy (1); Czech Republic (1)	105 (including 41 from Fiegl <i>et al.</i> [2006])	2 (1–8)	Efficacy	43 (4)	32.8	7	
Fiegl <i>et al.</i> [2011]	2002–2007	Austria (16); Italy (1); Czech Republic (1)	30	4 (2–12)	Efficacy	47	20	6.3	All retreatments
Ursuleac <i>et al.</i> [2011]	2006–2010	Romania (1)	44 (37 CLL)	Nr	Toxicity	nr	nr	nr	CMV-R in 8: 2 deaths; 6 sepsis deaths; 5 hemorrhagic deaths
Vallejo <i>et al.</i> [2011]	nr	Spain (nr)	102 (89 CLL)	nr	CMV-R rates	nr	nr	nr	39% CMV-R overall; 75% CMV-R with cumulative dose → 1000 mg
Cortelezzi <i>et al.</i> [2012]	2002–2009	Italy (11)	108	2 (1–6)	Efficacy and safety	56 (22)	39	19.4	7% serious infection rate
Total number treated			652 (623 CLL)						
Unless otherwise noted, all patients had chronic lymphocytic leukemia (CLL). CMV-R, cytomegalovirus reactivation; nr, not reported; OI, opportunistic infection.									

Recent use of alemtuzumab has focused on taking advantage of its activity in patients with *TP53* deletion and its primary effect on circulating disease. A rational combination would add an agent that targets lymph node disease to alemtuzumab's effect on circulating disease. For example, a current trial is investigating this strategy as a pre-transplant induction regimen in patients with *TP53* deletion [ClinicalTrials.gov identifier: NCT01465334]. With this regimen patients receive upfront treatment with ofatumumab in combination with high-dose methylprednisolone to reduce lymph node disease followed by ofatumumab in combination with alemtuzumab to eliminate residual circulating disease.

Another potential rational combination is to block the B-cell receptor pathway using a phosphoinositide 3 kinase (PI3K) inhibitor or a Bruton's tyrosine kinase (BTK) inhibitor, in combination with alemtuzumab. Targeting the B-cell receptor pathway in CLL has resulted in dramatic preclinical and early clinical responses [Fruman and Rommel, 2011; Hoellenriegel *et al.* 2011; O'Brien *et al.* 2011, 2012]. GS-1101 (formerly CAL-101; Gilead Sciences, Cambridge, UK), a PI3K δ isoform-specific inhibitor and ibrutinib (formerly PCI-32765, Pharmacyclics, Sunnyvale, CA, USA), a BTK inhibitor, have generated particular enthusiasm. Patients have a significant decrease in lymph node size with initiation of treatment and a transient increase in lymphocytosis. It is thought that a major mechanism of action of these drugs is interruption of B-cell receptor signaling, which causes CLL cells to leave the protective lymph node niche, resulting in an increased rate of apoptosis [Hoellenriegel *et al.* 2011; Lannutti *et al.* 2011; Herman *et al.* 2011; De Rooij *et al.* 2012; Ponader *et al.* 2012]. Given the single-agent activity of PI3K inhibitors and BTK inhibitors, they are now also being evaluated in combination trials [ClinicalTrials.gov identifiers: NCT01569295, NCT01539512, NCT01520519, NCT01611090]. One rational approach would be to use B-cell receptor signaling inhibition to promote migration of CLL into the circulation followed by treatment with alemtuzumab to increase clearance of the circulating tumor.

Conclusion

Alemtuzumab should be considered a standard part of the armamentarium used in the treatment of CLL [Skoetz *et al.* 2012]. Alemtuzumab is an FDA-approved agent for both upfront and

relapsed/refractory disease, although in clinical practice it appears to be reserved for patients who have progressed after multiple other lines of therapy. Early observations regarding increased activity on circulating disease relative to nodal disease have been confirmed in subsequent clinical trials. The efficacy observed in the initial intravenous trials has been duplicated with subcutaneous administration with a decrease in infusion-related toxicity. A large series of phase II trials has demonstrated that alemtuzumab has single-agent activity in CLL that is refractory to both alkylating agents and purine analogues, suggesting an independent mechanism of action. This unique mechanism allows for activity in patients with mutations of *TP53*, the CLL population with the worst prognosis.

Combination trials hold great potential for the induction of lasting remissions. However, the recent experience of increased mortality of FCA relative to FCR in first-line treatment, and the excess mortality in patients receiving alemtuzumab following rituximab and fludarabine demonstrate the potential toxicities of alemtuzumab. Future trials are attempting to capitalize on the unique attributes of alemtuzumab to improve efficacy without promoting additional toxicity. In particular, B-cell receptor signaling inhibitors, which cause a migration of CLL into the periphery, hold great promise as rational agents to add to alemtuzumab with minimal additional infectious risk.

Despite its efficacy, the widespread use of alemtuzumab has been limited somewhat by its infectious complications. Treatment guidelines recommend the use of viral and PCP prophylaxis and aggressive monitoring for CMV reactivation, as well as maintenance of neutrophil count with growth factors. Using this strategy, infectious complications can be prevented in a significant number of patients.

The optimal timing of alemtuzumab in a sequence of treatment regimens directed against refractory and relapsed CLL continues to be established. It is notable that in the recently published phase III trial [Elter *et al.* 2011], ORR did not differ significantly between the two arms, whereas the alemtuzumab arm clearly had improved median PFS and OS. As with many other types of cancer, the surrogate marker of ORR may not be truly informative in CLL, especially in the relapsed and refractory setting. Given that there is a significant

tradeoff in immediate and delayed toxicities, more robust PFS and OS information is needed to further elucidate alemtuzumab's role in the clinic. This caveat aside, alemtuzumab should be considered in patients with disease that is refractory to alkylating agents and purine analogues and maintains its activity independent of *TP53* mutational status. Alemtuzumab is most effective on circulating disease. Future trials should focus on combining alemtuzumab's distinct activity with agents that target lymph node disease and can contribute to the migration of nodal disease into the periphery.

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