# Alemtuzumab in the up-front setting

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**Abstract:** Alemtuzumab is a humanized chimeric monoclonal antibody targeting CD52. Although this agent already has an important role in the treatment of chronic lymphocytic leukemia (CLL), many of its uses are still being defined. Early trials showed alemtuzumab's value in refractory disease and helped to define its excellent activity in the bone marrow, spleen and 17p deleted patients. The CAM307 trial has demonstrated alemtuzumab's efficacy as monotherapy in the front-line setting, and ultimately led to its FDA approval as frontline therapy. Especially promising is the trend toward improved response in patients with high risk cytogenic abnormalities (17p del, 11q del, trisomy 12). The various consolidation trials have also provided promising results of achieving eradication of minimal residual disease (MRD). Although the ultimate benefit of achieving MRD negativity remains under investigation, alemtuzumab's potent activity on the bone marrow will likely make it an important part of combination therapy.

**Keywords:** alemtuzumab, chronic lymphocytic leukemia, consolidation, minimal residual disease, 17p deletion, 11q deletion

## Introduction

Alemtuzumab is a humanized chimeric monoclonal antibody targeting CD52. Although this agent already has an important role in the treatment of chronic lymphocytic leukemia (CLL), many of its uses are still being defined. Most experience using alemtuzumab has been in the relapsed and refractory setting. Its initial FDA approval in CLL was based on a pivotal trial of 93 fludarabine-refractory patients (Keating et al 2002). Alemtuzumab's particularly good activity in high risk patients at clearing peripheral blood, bone marrow and spleen of CLL cells have led to its consideration in the first-line setting. The impressive results of a recent study, the CAM307 trial, have led to alemtuzumab's approval for up-front use in CLL. Despite its approval in both upfront and relapsed settings, alemtuzumab's role in CLL treatment continues to evolve.

## The case for alemtuzumab in the up-front setting

Ample evidence of alemtuzumab's efficacy in difficult patient populations and in specific disease scenarios have ultimately led to its examination in the front-line setting. In 1997, Osterborg et al (1997) published the results of a European, multi-center trial in 1997 using single-agent alemtuzumab in 29 CLL patients who had relapsed after first-line treatment or who had refractory disease. The overall response rate was 41% and complete response was 4%. Its efficacy at clearing CLL cells from the peripheral blood (97% of patients) and from the bone marrow (36% of patients) was particularly notable. In addition, splenomegaly completely resolved in 32% of patients. On the other hand, lymph nodes were reduced to normal in only 2%. Rai et al (2002a) published a study in which 24 fludarabine-refractory patients received single-agent alemtuzumab and obtained a response-rate of 33% (there were no complete responses). Also in 2002, Keating et al (2002) published data from the CAM211 trial in which 93 fludarabine-refractory patients received alemtuzumab and achieved a 33% overall response rate.

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**Table 1** Alemtuzumab monotherapy trial in front-line setting

| Study | Patients | Regimen | Response rate | Complete response | Median progression-free survival |
|---|---|---|---|---|---|
| Osterberg et al (1996) single arm pilot study | n = 9 | Alemtuzumab 30 mg TIW for 18 weeks (4 patients received SQ; 5 patients received IV) | 89% (n = 8) | 33% (n = 3) | |
| Lundin et al (2002) phase II single arm study | n = 41 | Alemtuzumab 30 mg TIW for 18 weeks SQ | 87% (n = 38) | 19% (n = 7) | |
| Hillmen et al (2006) | n = 297 for entire trial; n = 149 for alemtuzumab arm | Alemtuzumab 30 mg TIW for 12 weeks | Alemtuzumab arm 83% (n = 124) | Alemtuzumab arm 24% (n = 36) | Alemtuzumab arm = 21.7 months |
| CAM307 Phase III study of alemtuzumab vs chlorambucil | n = 148 chlorambucil arm | Chlorambucil 40 mg/m$^2$ PO q28 days for max 12 cycles | Chlorambucil arm 55% (n = 82) | Chlorambucil arm 2% (n = 3) | Chlorambucil arm = 12.5 months |

Further evidence to help define alemtuzumab's role in high risk patients was shown in a study by Stilgenbauer et al (2002) in 2002. A response rate of 54% was achieved in fludarabine-refractory patients with the unfavorable mutation 17p deletions or p53 abnormalities. A subsequent trial performed by Lozanski et al (2004) found a 31% response in patients with this high-risk profile.

Alemtuzumab's use in combination with other agents also showed impressive results in refractory disease. The combination of alemtuzumab and fludarabine was examined in trials published by Kennedy et al (2002) (n = 6) and Elter et al 2005) (n = 36). Both studies found an overall response rate of 83%. Faderl et al (2003) used alemtuzumab in combination with rituximab in this population and achieved a response rate of 63%. This history of success in these profiles of high-risk populations, particularly with p53 deletions, extensive marrow disease with high peripheral lymphocyte counts, and without bulky lymph nodes, led investigators to examine roles for alemtuzumab in the up-front setting.

## Alemtuzumab monotherapy in the first-line setting

Use of alemtuzumab as monotherapy in CLL in the first-line setting was first reported by Osterborg et al (1996) in a pilot study of 9 patients (Table 1). Five received intravenous and 4 received subcutaneous alemtuzumab at a dose of 30 mg 3 times/week for a maximum of 18 weeks. Five patients achieved a partial remission and 3 achieved a complete remission. Duration of response ranged from 8 to 24 months. A phase II study was published in 2002 (Lundin et al 2002). Single-agent alemtuzumab was administered subcutaneously thrice weekly for 18 weeks to 41 patients as first-line treatment. Thirty-eight patients responded to therapy, for an overall response rate of 87 % ( 95% CI, 76%–98%) – 19% achieved a complete remission and 68% achieved a partial remission. 95% of patients cleared CLL cells in their peripheral blood at a median of 21 days of treatment, and 66% achieved CR or nodular PR in the bone marrow after the full course of 18 weeks of treatment. The treatment was generally well-tolerated with neutropenia (21%) and cytomegalovirus (CMV) reactivation (10%) being the most serious toxicities. There were transient injection-site skin reactions in 90% of patients.

## The CAM307 trial

Results of an international prospective, randomized, controlled trial comparing alemtuzumab to chlorambucil as front-line therapy was reported at the American Society of Hematology annual meeting in 2006 (Hillmen et al 2006) and published in December 2007 (Hillmen et al 2007). A total of 297 patients were accrued, and were randomized to receive either alemtuzumab (n = 149) 30 mg IV thrice weekly for up to 12 weeks or chlorambucil (n = 147) 40 mg/m$^2$ PO every 28 days for a maximum of 12 cycles. The primary endpoint was progression-free survival (PFS) and secondary endpoints were response rate, overall survival, and safety.

The alemtuzumab arm showed an overall response rate of 83% compared to a 55% response rate in the chlorambucil arm. Complete responses were seen in 24% and of the alemtuzumab arm and 2% of the chlorambucil arm. MRD negativity was achieved in 11 of 36 complete responders in the alemtuzumab arm vs none in the chlorambucil arm. Time to alternative treatment was 23.3 months for the alemtuzumab arm vs 14.7 months for the chlorambucil arm ($p = 0.0001$).

**Table 2** Alemtuzumab consolidation trials

| Study | Patients | Regimen | Response rate | MRD negativity | Median progression-free survival/ survival |
|---|---|---|---|---|---|
| O'Brien et al (2003) Alemtuzumab consolidation with 10 mg vs 30 mg doses | n = 41 | Alemtuzumab given after fludarabine induction in the following doses: 10 mg IV TIW for 4 weeks (n = 24); or 30 mg IV TIW for 4 weeks (n = 34) | Improved response after induction all patients = 46% (n = 19): 30 mg arm = 56% 10 mg arm = 39% | 38% (11 of the 29 patients tested for MRD) | Not reached at median follow of 18 months |
| Wendtner et al (2003) phase III trial of alemtuzumab vs observation following fludarbine-based therapy | n = 21 | Alemtuzumab 30 mg SQ TIW consolidation vs observation following a response to fludarabine-based therapy | (18%) 2 of 11 on alemtuzumab arm had improved response over induction | 83% (5 of 6 patients tested for MRD in peripheral blood) | Alemtuzumab arm: not reached at median follow up of 21.4 months. Observation arm: 24.7 months |
| Moreton et al (2005) Treatment of fludarabine-refractory patients to best possible remission | n = 91 | Alemtuzumab 30 mg TIW (SQ or IV) until maximum response (median 9 weeks) | 53% (n = 49) overall response rate. 36% (n = 32) had CRs | 20% (n = 18) | Overall survival for MRD– patients not reached. Overall survival for MRD+ patients with CRs had a median survival of 41 months. |
| CALGB (2003) Alemtuzumab following fludarabine in previously untreated patients | n = 24 | Alemtuzumab 30 mg SC for 6 weeks following fludarabine | 66% overall response (12 of 18 patients who received alemtuzumab); 22% CR; 44% PR | | |
| Montillo et al (2004) phase II study of alemtuzumab following clinical response to fludarabine | n = 34 | Alemtuzumab 10 mg SC for 6 weeks following response to fludarabine | 53% (18 of 34) patients had improved response over induction | 56% (n = 19) | |

**Abbreviations:** CR, complete response; MRD, minimal residual disease; PR, partial response.

Especially notable was that these benefits were particularly evident in patients with high-risk cytogenetic abnormalities. Of the 282 patients who had cytogenetic analysis, 231 patients (82%) revealed abnormalities, including 19% with 11q deletions, 7% with 17p deletions and 14% with trisomy 12 (Robak et al 2006). Patients with 17p deletions who were treated with alemtuzumab had a PFS of 10.7 months compared to 2.2 months for patients who received chlorambucil. Overall response rates for these two groups were 64% and 20%, respectively. Patients with 11q deletions had response rates of 87% and 29% in the alemtuzumab and chlorambucil arms, respectively. PFS was 8.5 months in both arms. Similarly, patients with trisomy 12 had a PFS of 18.3 months vs 12.9 on the alemtuzumab and chlorambucil arms, respectively. These two groups had similar response rates of 83% in the alemtuzumab arm and 80% in the chlorambucil arm. Of particular note, however, is that although these benefits for patients with high risk cytogenetics were statistically significant in terms of response, this did not extend to PFS. Although there was a trend of increased PFS in the 17p group treated with alemtuzumab, it did reach statistical significance.

In terms of toxicities, the incidence of grade 3 and 4 neutropenia occurred in 45% of the alemtuzumab arm vs 26% of the chlorambucil arm. Infectious complications were reported in 76% of patients on the alemtuzumab arm compared to 50% on the chlorambucil arm. CMV viremia occurred in 52% of patients on the alemtuzumab arm and 16% had symptomatic CMV infections. Only 7.5% of patients on the chlorambucil had evidence of CMV viremia by PCR, none of whom were symptomatic.

Although this trial adds important data in terms of the use and activity of alemtuzumab as single-agent in the front line, the results must be cautiously interpreted due to its relatively short median follow-up of only 24.6 months, and the fact that 84% of patients in each arm remain alive. Nevertheless, the trial adds particularly useful data in terms of approach to 17p deleted patients, and may ultimately contribute to the creation of a new standard of care for these patients.

## Alemtuzumab consolidation

Although alemtuzumab has been shown to be less effective treating bulky lymph nodes, multiple studies have demonstrated its utility in clearing the blood and bone marrow of disease (Dyer et al 1997; O'Brien et al 2003). Based on these observations, alemtuzumab has been used in several trials as consolidation therapy to eradicate minimal residual disease (MRD) in the bone marrow after initial therapy with other agents to debulk peripheral lymph nodes (Table 2).

In 1997 Dyer et al (1997) published a small study of 6 CLL patients who were treated with fludarabine, had persistent disease in the bone marrow, and then were treated with alemtuzumab. Five of the 6 patients achieved a hematologic and histological complete remission following alemtuzumab. O'Brien et al (2003) further examined the concept of eradication of MRD in a series of 41 patients. Forty-six per cent of the patients overall, and 56% of those patients that received the 30 mg dose (n = 17) had improvement in their disease-response after the alemtuzumab treatment. Eleven (38%) of the 29 patients whose bone marrow was tested by two-color flow cytometry achieved a flow-negative remission. At a median follow-up of 18 months, 6 patients remained disease-free (24–48 months after therapy) and median time to disease progression had not yet been reached at the time of their report or until 18 months median follow-up. Fifteen patients (37%) were reported to have infectious complications, 9 of which were CMV reactivations.

At the annual meeting of the American Society of Clinical Oncology in 2005, Wendtner et al (2004) and the German CLL Study Group presented the results of a trial that randomized patients who responded to fludarabine/cyclophosphamide or fludarabine alone to either alemtuzumab 30 mg subcutaneous 3 times per week for 12 weeks or observation. The trial was ultimately stopped early due to severe infectious toxicities. Of the 21 evaluable patients, 11 were randomized to receive alemtuzumab. Patients in the alemtuzumab arm showed a significantly longer PFS compared to those in the observation arm (no progression at a median of 21.4 months follow up vs 24.7 months). Seven of the 11 patients on the alemtuzumab arm had infectious complications including one life-threatening case of pulmonary aspergillosis, 4 patients with CMV reactivation (2 with clinically evident CMV pneumonia), 1 tuberculosis and 1 herpes zoster infection.

Moreton et al (2005) published a larger study in 2005 using alemtuzumab in consolidation. Although these patients were previously treated, consolidation proved to be an attractive concept in the front-line setting as well. Ninety-one patients received alemtuzumab for a median of 9 weeks. Thirty-six per cent obtained a complete remission, including 20 % (n = 18) who had obtained MRD negativity by flow cytometry. Of note, the patients who achieved MRD negativity had a significantly prolonged treatment-free survival compared with patients with MRD positivity but with a clinical complete response (CR) (median treatment-free survival not reached vs 20 months, respectively ($p < 0.0001$). MRD negative patients had not reached median overall survival vs median overall survival of 60 months for those patients that obtained CR but not MRD negativity. This study helped to initiate discussion as to whether or not MRD negativity should be a new goal of treatment (Montserrat 2005). It remains unclear as to whether achievement of MRD-negativity itself results in a better outcome, or if the ability to clear the bone marrow simply represents a group of patients with more sensitive disease. The issue is still being debated.

The Cancer and Leukemia Group B (CALGB) conducted a study using alemtuzumab following fludarabine in the first-line (Rai et al 2002b, 2003). Fifty-six patients were enrolled and received 4 monthly cycles of single-agent fludarabine. Patients that achieved stable disease or better after 2 months of observation following fludarabine received alemtuzumab 30 mg intravenously TIW for 6 weeks, intravenously. Another 24 patients underwent the same fludarabine regimen, but received alemtuzumab subcutaneously if a response was achieved. In the first group (designated to receive intravenous alemtuzumab), 36 of the 56 patients ultimately received alemtuzumab IV. Fifteen of those 36 improved to CRs (42%) and 18 had PRs (50%) for an overall improvement of response rate to 92%. Of the 24 patients in the second (subcutaneous alemtuzumab) group, 18 patients qualified to get subcutaneous alemtuzumab. Of those 18 patients, 12 (66%) improved their response, including 22% who achieved CRs and 44% who achieved PRs.

Mantillo et al also examined the achievement of MRD negativity following alemtuzumab consolidation in a phase II study of 34 patients (Montillo et al 2006). Patients who had a clinical response to fludarabine-based therapy in the front-line received alemtuzumab 10 mg subcutaneously TIW for 6 weeks. Patients went on to have stem cell mobilization for transplant. Following treatment with the alemtuzumab, the CR rate improved from 35% after the fludarabine treatment to 79%. Nineteen patients (56%) achieved MRD negativity. There was CMV reactivation in 18 patients, all of whom were successfully treated with antiviral therapy.

Twenty-four of these patients underwent successful stem cell collection and 18 underwent autologous bone marrow transplant.

## Infectious toxicities of alemtuzumab

Alemtuzumab has well-known infectious complications. As described in the pivotal trials above, major infectious complications were observed in approximately half of the patients (Keating et al 2002; Rai et al 2002a). These infections included septicemia, opportunistic infections such as aspergillosis, *Pneumocystis carinii*, herpes simplex (re)activations, and cytomegalovirus. Generally, these infectious complications have been found to be more common in patients who are not responding to alemtuzumab thereapy (Rai et al 2002a; Montillo et al 2006). In one study, Rai et al found major infections in only 2 of 8 responders, compared with 8 of 16 nonresponders. A retrospective evaluation of 27 patients treated for lymphoid malignancies at Dana Farber/Brigham and Women's Hospital found that 56% (15 of 27) experienced opportunistic infections (including CMV(44%), progressive multifocal leukoencephalopathy, adenovirus, toxoplasmosis, and acanthamaebiasis). In addition, 30% nonopportunistic infections were found in 22 patients (Martin et al 2006). These complications are particularly common when alemtuzumab is combined with purine analogs (Keating et al 2002).

Cytomegalovirus (CMV) infection is the most common complication. In the CAM307 trial, 52.4% of patients receiving alemtuzumab have asymptomatic positive CMV by PCR vs 7.5% of the patients who received chlorambucil. An additional 15.6% of patients on the alemtuzumab arm had symptomatic CMV involvement (Hillmen et al 2007).

Close monitoring of CMV copies by PCR during treatment with alemtuzumab allows for detection of asymptomatic reactivation. There should be high suspicion of CMV infection in any patient with unexplained fever, increase in LFTs or respiratory symptoms, even with no detectable CMV in the blood. Typically, if CMV is detected, or if there is a high suspicion on infection, alemtuzumab is temporarily held and antiviral therapy is initiated. Some debate does exist as to what point alemtuzumab should be held and restarted. Published guidelines by O'Brien et al (2006) suggest that alemtuzumab be held only in the setting of severe infection or persistent symptoms.

Once signs and symptoms of infection have resolved, the therapy should be restarted. Both symptomatic and asymptomatic CMV in these patients usually responds to gancyclovir. Prophylaxis for prevention of varicella zoster and herpes simplex reactivation, as well as for pneumocystis carinii pneumonia, should also be given throughout treatment. These prophylactic antibiotics and CMV monitoring should be continued following alemtuzumab for approximately 6–8 months, and at least until recovery of CD4+ T-cells.

## Conclusion

Alemtuzumab's role continues to expand. Early trials showed alemtuzumab's value in refractory disease and helped to define its excellent activity in the bone marrow, spleen and 17p deleted patients. With this data, additional trials were developed in an attempt to further expand its role. The CAM307 trial has demonstrated alemtuzumab's efficacy as monotherapy in the front-line setting. Especially promising is the trend toward improved response in patients with high risk cytogenic abnormalities (particularly 17p del). This trend requires further investigation but notwithstanding, alemtuzumab is a reasonable first-line choice for this population. The various consolidation trials have also provided promising results of achieving eradication of minimal residual disease (MRD). Although the ultimate benefit of achieving MRD negativity remains under investigation, alemtuzumab's potent activity on the bone marrow will likely make it an important part of combination therapy.

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