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## Minimal residual disease elimination by consolidation therapy with alemtuzumab

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Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies in the developed world. In recent decades, the development of novel therapies has greatly expanded the range of treatment options, including monoclonal antibodies. New methods for detecting residual disease have also been developed and are being used to assess the depth of clinical response achieved with novel treatment strategies.

One such strategy involves the use of the monoclonal antibody as consolidation therapy to eradicate minimal residual disease (MRD) following chemotherapeutic induction. Alemtuzumab is a humanized monoclonal antibody that binds CD52, an antigen expressed at high density on most normal and malignant T- and B-cell lymphocytes but not on hematopoietic stem cells.<sup>1,2</sup>

Alemtuzumab has demonstrated consistent activity against malignant lymphocytes in blood, marrow and the spleen. However, its activity is limited by the presence of bulky disease (lymph nodes, extranodal masses), which is often associated with refractory disease. The suggestion that monoclonal antibodies, such as alemtuzumab, might be best utilized under conditions of MRD has prompted several trials investigating the role of alemtuzumab following tumor debulking by chemotherapy.

### **Phase II consolidation trials with alemtuzumab**

Montillo *et al.*<sup>3,4</sup> administered subcutaneous (s.c.) alemtuzumab, up to 10 mg three times weekly for 6 weeks, to 30 patients, who had responded to fludarabine induction but who had persistent bone marrow disease that precluded stem cell harvest and subsequent autologous stem cell transplantation (SCT). There was a median of 5 months (range 2–11 months) between the completion of induction and the initiation of consolidation to allow hematologic recovery. Montillo *et al.*<sup>3</sup>

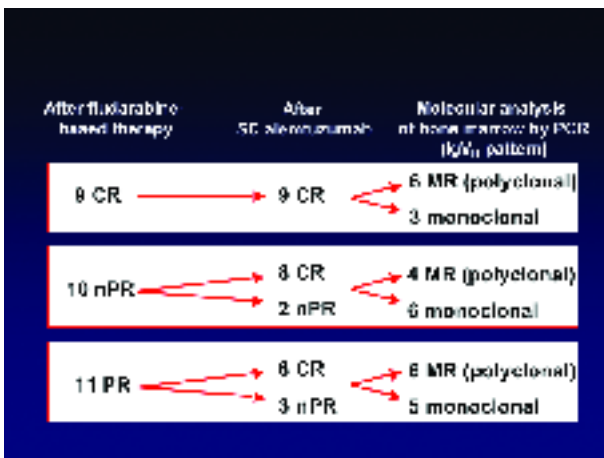
selected the s.c. route of administration because adverse reactions have been shown to be rarer and milder with this mode of administration than with intravenous (i.v.) administration of alemtuzumab.<sup>5,6</sup>

Eighty-seven per cent of patients improved their responses following alemtuzumab consolidation (Figure 1), with 16 (53%) patients achieving bone marrow molecular remission (MR) by consensus polymerase chain reaction (PCR). Six of 9 patients in complete remission (CR) after fludarabine induction converted to MR after alemtuzumab consolidation, 8 of 10 patients in nodular partial responses (nPR) after fludarabine induction converted to CR, including four MR, whereas 9 of 11 patients in partial remission (PR) after fludarabine induction improved their responses to either nPR (n=1) or CR (n=8), including six MR. Fifteen of 16 patients successfully mobilized peripheral blood stem cells (granulocyte colony-stimulating factor [G-CSF] + intermediate-dose cytarabine), and 10 patients proceeded to autologous transplant. At a median of 7 months follow-up (range 1–24 months), none of the transplanted patients had progressed.

Subcutaneous alemtuzumab was generally very well tolerated (Figure 2); adverse reactions were limited to NCI grade 1/2. The most common events were local skin reactions and fever. There were no new cases of thrombocytopenia or anemia during treatment, and only two patients developed grade 2 neutropenia, which resolved quickly after G-CSF administration. No non-viral infectious episodes were recorded. However, cytomegalovirus (CMV) PCR screening identified CMV reactivation in 15 (50%) patients; prompt treatment with oral ganciclovir prevented CMV disease in all cases.

Some authors question whether specific antiviral therapy is required for previously treated patients with CLL receiving alemtuzumab therapy who show only CMV antigenemia and/or PCR positivity, considering the very low incidence of CMV symp-

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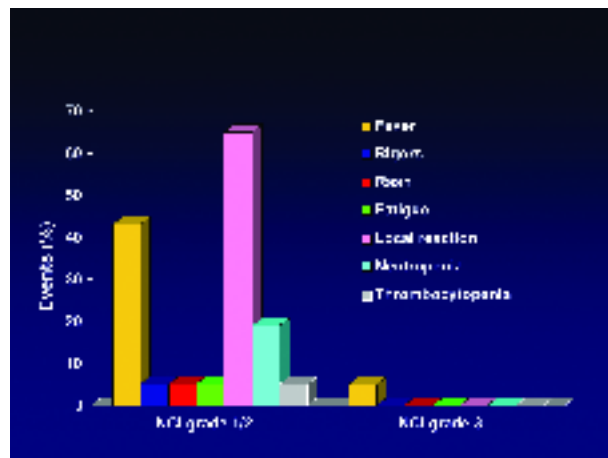


**Figure 1. Achievement of molecular response after consolidation therapy with subcutaneous alemtuzumab following fludarabine induction.<sup>4</sup>**

toms or CMV disease.<sup>7</sup> Most research on CMV reactivation has been carried out in patients receiving SCT,<sup>8-11</sup> and the introduction of viral load assays has enabled risk stratification in SCT patients according to initial viral load and increases in viral load.<sup>12</sup> However, the CMV viral load required for CMV reactivation is less clear in other groups of patients because of a lack of data. As patients are severely immunocompromised following SCT, the CMV load required to cause disease is likely to be higher in patients treated with alemtuzumab following chemotherapeutic induction. PCR screening may, therefore, be required only when patients are symptomatic with unexplained fever: studies are underway to determine whether there is a clinically significant viral load for predicting disease in these patients.

The study by Montillo *et al.*<sup>4</sup> demonstrated that consolidation therapy with alemtuzumab following fludarabine induction was feasible and well tolerated. Stem cell mobilization was not compromised, allowing patients to proceed to autologous SCT. The treatment proved highly effective in improving the quality of response achieved after induction and in purging residual tumor cells from the bone marrow.

O'Brien *et al.*<sup>13,14</sup> provided further evidence for the effectiveness of alemtuzumab in eradicating MRD following chemotherapy induction. A total of 58 heavily pretreated patients in PR, nPR or CR with detectable MRD following chemotherapy induction received i.v. alemtuzumab consolidation, 10 mg or 30 mg three times weekly for 4 weeks. The median age of the patients was 60 years (range 44-79 years) and the median number of prior treatments was 2 (range 1-7). The initial treatment schema of 10 mg three times weekly for 4 weeks was changed after analysis to 30 mg three times weekly for 4 weeks to



**Figure 2. Adverse events summarized for consolidation therapy with subcutaneous alemtuzumab following fludarabine induction.<sup>4</sup>**

increase response rates. Anti-infective prophylaxis was given for herpes (valacyclovir) and *Pneumocystis carinii* (trimethoprim-sulfamethoxazole) during therapy with alemtuzumab and for 2 months post-therapy.

Following chemotherapy induction, the response status prior to alemtuzumab was 6 (10%) CR, 33 (57%) PR, and 19 (33%) nPR. It was expected that residual lymphadenopathy, if present, would be small in volume, and that assessing a PR (50% reduction in small-volume disease) would be difficult to measure. Thus, to consider patients with lymphadenopathy as responders to alemtuzumab, their disease status was required to convert to a CR or nPR, as defined by NCI criteria. Only residual disease in bone marrow was permitted. For patients in nPR at the initiation of therapy, response to alemtuzumab was defined as a conversion to CR.

Overall, 53% of the patients responded to alemtuzumab therapy: 9 of the 23 (39%) patients treated with 10 mg alemtuzumab responded, compared with 17 of the 26 (65%) patients treated with 30 mg alemtuzumab ( $p=0.066$ ). Nine of 19 patients in nPR achieved a CR and 12 of 26 patients in PR improved to nPR or CR. The major reason for failure to improve response was residual lymphadenopathy. Residual bone marrow disease cleared in most patients and 11 of 29 (38%) patients achieved a molecular remission (PCR pending on other patients). The median time to progression (TTP) was much better than expected in these patients, with the median TTP not reached in responders at a median follow-up of 24 months. Six patients were still in remission between 30 and 44 months after therapy. When patients were analyzed according to their PCR status after alemtuzumab, patients who had positive PCR results had

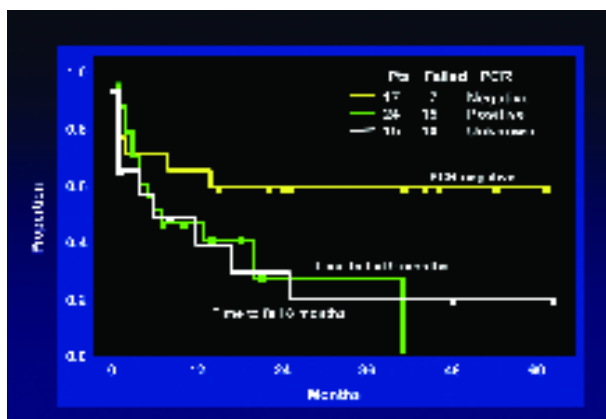


Figure 3. Time to failure according to PCR status following alemtuzumab consolidation.<sup>13,14</sup>

a median TTP of 9 months, patients who lacked PCR data had a median TTP of 9 months, and the median TTP for patients with negative PCR results had not been reached (Figure 3).

Mild to moderate infusion-related events (predominantly fever and chills) were common with initial alemtuzumab doses. The infection rate was very low, with infections occurring in only 15 patients and consisting mostly of symptomatic CMV reactivation in 12 (20%) patients. Three patients developed Epstein-Barr virus-positive large cell lymphoma, which was an unexpected finding in this setting. Two patients showed spontaneous resolution and one resolved following treatment with cidofovir and i.v. immunoglobulin, suggesting that additional chemotherapy should be given cautiously in patients with lesions following alemtuzumab consolidation, as the lesions may regress spontaneously.

#### CALGB 19901 trial in patients with untreated CLL

The CALGB 19901 trial of fludarabine induction and alemtuzumab consolidation was carried out in patients with untreated CLL.<sup>15,16</sup> The trial began initially with i.v. delivery of alemtuzumab, but was subsequently amended to administer s.c. alemtuzumab. Following fludarabine induction, there was a 2-month observation period for hematologic recovery before patients achieving stable disease (SD), or better, were eligible to receive 6 weeks of s.c. alemtuzumab.

Figure 4 summarizes the response data, but it should be noted that the study should not be used to compare s.c. with i.v. administration of alemtuzumab, as the overall response following fludarabine induction in the group that received i.v. alemtuzumab was 56% compared with 36% in the group that received s.c. alemtuzumab. It is possible only to conclude that, whether administered as either a s.c. or an i.v. injection, alemtuzumab provides good consolidation responses.

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The safety profile of s.c. alemtuzumab was better than that of i.v. alemtuzumab. With i.v. administration of the monoclonal antibody, infusion-related reactions were common though mostly mild (grade 1/2), and 12 of 36 patients developed grade 3 infections during or after alemtuzumab, 8 of which were CMV reactivations (6 resolved, 1 persistent, 1 fatal). Local skin reactions were most common with s.c. alemtuzumab, but were mild (grade 1/2). CMV reactivation was observed in three of 18 patients, but there were no deaths.

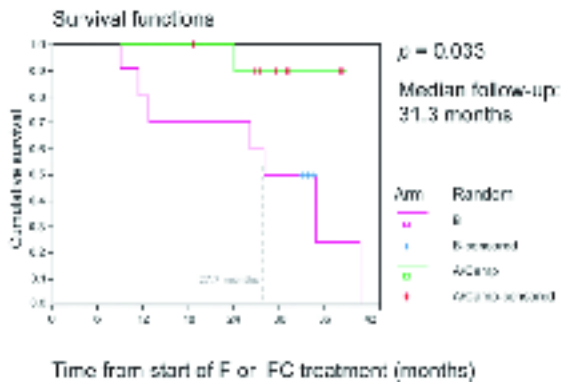
#### Phase III trial of alemtuzumab consolidation in patients with CLL in first remission

Following the promising results of phase II trials of alemtuzumab consolidation, a phase III trial was initiated, in which patients in remission following first-line therapy with fludarabine or fludarabine + cyclophosphamide (FC) were randomized to receive standard-dose alemtuzumab consolidation (30 mg i.v. three times weekly for 12 weeks, n=11) or no further treatment (observation arm, n=12).<sup>17,18</sup> The primary endpoint was progression-free survival (PFS), with secondary endpoints being response rates (NCI criteria), the presence or absence of MRD, and safety. Anti-infective prophylaxis (trimethoprim-sulfamethoxazole and either famciclovir, valacyclovir, or acyclovir) was given during treatment and for at least 2 months following discontinuation of alemtuzumab therapy. MRD was determined by quantitative allele-specific IgVH real-time PCR with peripheral blood sampling.

Twenty-three patients were enrolled, of whom 21 were evaluable, with a median age of 60 years (range 37–66 years). Eleven of the 21 evaluable patients were

	IV alemtuzumab (n = 11)	SC alemtuzumab (n = 24)
<b>Induction</b> 4 cycles fludarabine 28 mg/m <sup>2</sup> days 1–5	CR: 45% OR: 56%	CR: 45% OR: 36%
<b>Consolidation</b> 6 weeks alemtuzumab 30 mg TW	CR: 42% OR: 32%	CR: 22% OR: 66%
<b>Overall</b> (induction + consolidation)	CR: 27% OR: 70%	CR: 10% OR: 50%

Figure 4. Response data summarized for CALGB 19901.<sup>15,16</sup> The different response rates obtained following fludarabine induction alone mean that the response rates for induction followed by alemtuzumab consolidation should not be compared with respect to subcutaneous and intravenous administration routes.



**Figure 5. Progression-free survival (PFS) following alemtuzumab consolidation from the time-point of randomization to alemtuzumab treatment or observation only (no treatment).**<sup>17,18</sup>

randomized to alemtuzumab.

The primary endpoint, PFS, as measured from the start of chemotherapy, was significantly longer with alemtuzumab consolidation at a median of 31.3 months of follow-up compared with no further treatment (no progression vs. a mean of 27.7 months,  $p=0.033$ ). At this time point, there had been only one relapse in the alemtuzumab arm compared with 7 of 10 in the control arm. Similarly, the PFS determined from the actual point of randomization to alemtuzumab or no treatment (median 25.2 months) was significantly increased in the alemtuzumab group (no progression vs. 20.6 months,  $p=0.04$ ) (Figure 5).

There was a trend towards improved response rates (CR and PR) in patients who received alemtuzumab therapy (11/11 vs. 7/10,  $p=0.059$ ) 6 months after randomization (Figure 6). Two patients converted to CR in the alemtuzumab-treated group, whereas three patients progressed in the observation arm. Five of 6 patients achieved MR in peripheral blood in the alemtuzumab group whereas all patients in the observation arm remained MRD-positive ( $p=0.048$ ). None of the patients had achieved MR after fludarabine or FC treatment.

Using this treatment regimen, alemtuzumab consolidation was unexpectedly associated with a high incidence of infectious complications. After a median of 4 weeks, alemtuzumab treatment had to be halted due to severe infections in 11 patients (1 life-threatening grade IV pulmonary aspergillosis, 4 grade III CMV reactivations requiring i.v. ganciclovir, 1 grade III pulmonary tuberculosis reactivation, 1 grade III herpes zoster infection), and the trial was stopped prematurely.

The time interval between the last dose of fludarabine and the initiation of alemtuzumab was much shorter than that reported by O'Brien *et al.*,<sup>13</sup> with a

6 months post-randomization data			
Treatment arm	Post-fludarabine	6 months	MRD <sup>+</sup>
Alemtuzumab	1 CR 10 PR	3 CR 8 PR	6/6
No treatment	2 CR 3 nPR 5 PR	2 CR 2 nPR 3 PR 3 PD	0/3
			$p = 0.048$

**Figure 6. Six months post-randomization data from a phase III randomized trial of alemtuzumab consolidation compared with observation in patients with CLL.**<sup>17,18</sup>

median interval of only 67 days compared with the much longer time of 5 months (range 2-11 months) reported by O'Brien *et al.*<sup>13</sup> Both bone marrow and T-cell function may be impaired for several months following purine analog therapy,<sup>19</sup> so that a longer time interval between last chemotherapy and the start of alemtuzumab consolidation might be preferable.

### Discussion

The current standard approach to management of CLL is a *watch-and-wait* policy. If patients require treatment, they are treated until their best response is achieved and then observed until there is evidence of disease progression. Studies involving consolidation therapy with alemtuzumab have attempted to determine whether alemtuzumab therapy can eliminate residual disease following chemotherapy to debulk tumor. Alemtuzumab, with its differing mechanism of action, provides another method for killing tumor cells that may have been resistant to the induction agent.

The promising results observed with these studies suggest that alemtuzumab can be highly effective in purging residual disease following chemotherapy induction, with bone marrow disease more likely to be cleared than adenopathy. PCR negativity is achieved and may improve remission duration. Subsequent stem cell mobilization is not compromised, enabling patients to proceed to autologous SCT. However, doses for consolidation therapy may differ from those for conventional alemtuzumab treatment in relapsed CLL, with the outcome awaited from ongoing research to define the best dosing regimen. In addition, s.c. administration appears to be better tolerated than i.v. administration. However, the rate of infectious complications may be higher if the interval between induction and initiation of alemtuzumab is less than 3 months.

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