

Consolidation therapy with alemtuzumab prolongs remission of chronic lymphocytic leukaemia



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A B S T R A C T

The use of chemotherapeutic agents such as fludarabine has made it possible to treat chronic lymphocytic leukemia (CLL) more effectively than was previously possible with alkylating agents. However, relapse still occurs frequently as the disease can re-emerge from remnants of the malignant cell clone – referred to as minimal residual disease (MRD). Thus, the primary goal of consolidation therapy in CLL is to eradicate MRD and thereby alter the treatment goal from palliation to cure. Consolidation therapy with alemtuzumab following fludarabine or fludarabine-based chemotherapy can provide an improvement in the quality of clinical responses, an increase in progression-free survival, eradication of MRD, and molecular remission in more than one-third of patients with CLL. A treatment interval of 3 to 6 months between induction chemotherapy and alemtuzumab consolidation appears to minimize the risk of infectious complications. Ongoing trials will need to answer remaining issues regarding timing, schedule and dose of alemtuzumab consolidation therapy. Although alemtuzumab consolidation is not yet a treatment standard in CLL, this approach might bring us closer to the treatment goal of cure in CLL.

Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent form of adult leukemia in the Western world¹ and is characterized by the accumulation of functionally immature lymphocytes in the bone marrow, blood, lymph tissue, and other organs. Almost all CLL cases involve malignant B-lymphocytes, with 2–3% involving T cells.² Major symptoms of CLL include fatigue, night sweats, and decreased appetite/weight loss, but involvement of bone marrow also leads to a weakening of the immune system, exposing the patient to a higher risk of infection.^{3,4} On the basis of the presenting features, patients can be classified into low, intermediate or high clinical risk categories, and the

presence of other prognostic factors such as lymphocyte morphology and the lymphocyte doubling time, β 2-microglobulin and thymidine kinase levels, deletions or mutations of the p53 gene, and various chromosomal translocations may further refine the risk.⁵

Although the introduction of chemotherapeutic agents such as fludarabine has made it possible to treat CLL more effectively than was previously possible with alkylating agents, relapse is almost inevitable since the disease re-emerges due to the proliferation of residual malignant cells or minimal residual disease (MRD). Thus, even if 20–40% of previously untreated patients achieve complete remission (CR), the majority will relapse after a median period of 20 to 30 months.^{6,7} Consequently, the detection and eradication of

MRD is critical for the prevention of relapse and the achievement of long-term remission. Thus, treatment strategies must be able to eradicate MRD to the highest levels of detection currently available if they are to offer the possibility of a cure to patients with CLL.

The importance of minimal residual disease

As the definition of a CR by the current National Cancer Institute Criteria can allow up to 30% of cells to remain present in the bone marrow,⁸ the need has arisen for sensitive detection of low level disease. Moreton and colleagues took 91 patients responding to therapy and compared patients with measurable MRD to those in whom MRD could no longer be detected (MRD-negative CRs). They found that patients achieving a MRD-negative CR had statistically significantly longer PFS and OS compared with patients achieving a MRD-positive CR. Indeed, patients achieving a MRD-positive CR had a PFS and OS that were comparable to patients achieving a PR only.⁹

The use of polymerase chain reaction (PCR) techniques with consensus primers have been used to assess eradication of CLL and are based on the uniqueness of the immunoglobulin gene rearrangement; however, this approach is limited as consensus primers may be unable to amplify a product in 20% of cases and sensitivity can be diminished in the presence of polyclonal lymphocytes.¹⁰ The inclusion of allele-specific oligonucleotide (ASO) primers in PCR techniques (ASO-PCR) can help overcome these limitations with sensitivity corresponding to the detection of one malignant cell against a background of 10⁵ normal cells.¹¹

As an alternative approach to PCR, flow cytometry can be utilized to assess MRD levels and is based on an immunophenotypic response which involves separation of cells by

physical characteristics and expression of cell surface markers. Flow cytometric analyses are dependent on the detection of an excess of CLL cells in peripheral blood or bone marrow, with cell surface antigens able to identify the malignant clone, and peripheral blood or bone marrow cells are bound to monoclonal antibodies specific for these markers linked to fluorescent dyes. Use of multiple markers, along with the ability of flow cytometers to measure light scatter (roughly equivalent to particle size and cell granularity), improves the specificity of this detection technique. PCR with consensus primers (consensus PCR) is generally considered to be more sensitive than 2-color flow cytometry, although comparable to 3- and 4-color cytometry.¹² The most sensitive 4-color MRD-flow cytometry technique currently available (MRD-flow) is a variant of 4-color flow analysis which utilizes a specific sequential gating strategy.¹² MRD-flow has been compared with 4-color flow, 2-color flow and consensus PCR with relative sensitivities observed for detection of CLL cells (median percentage of total leukocytes) given as 0.005% as compared with 0.4%, 1.2% and 0.6%, respectively.¹²

Targeted monoclonal antibodies offer a promising addition to chemotherapy in refractory CLL. Alemtuzumab (Campath®; MabCampath®) is a humanized monoclonal antibody approved for use in CLL that offers proven efficacy in CLL patients who have failed on treatment with alkylating agents and fludarabine. Alemtuzumab has a different, p53-independent mode of action compared with conventional chemotherapy that leads to cell death through antigen-dependent cellular cytotoxicity, complement activation, and direct induction of apoptosis. It selectively targets the CD52 antigen present on lymphocytes, resulting in the removal of these cells from the blood, bone marrow, and other affected organs.

Clinical trials of consolidation therapy with alemtuzumab

The eradication of residual disease is associated with an improved duration of remission and has great potential in offering the possibility of cure for CLL. The primary goal of consolidation therapy in CLL is to eradicate MRD. Due to its ability to achieve clinical remissions and successfully purge MRD from both blood and bone marrow, the use of alemtuzumab is the foundation of many eradication-focused treatment approaches in CLL.

Data from several phase I-III clinical studies have consistently demonstrated an improvement in the number and quality of clinical responses with alemtuzumab consolidation therapy after fludarabine-based chemotherapy of CLL (Table 1). This suggests that alemtuzumab may prove to be the optimal drug for consolidation in patients that remain MRD-positive after an induction chemotherapy.

A phase II trial conducted at the M.D. Anderson Cancer Center (Houston, TX) utilized intravenous (IV) alemtuzumab in patients with CLL who had responded to fludarabine combination therapy (n=41; median age 60 years).¹⁵ Patients with a partial response (PR),

nodal partial response (nPR) or complete response (CR) after induction chemotherapy who had evidence of residual disease on immunophenotyping (2-color flow cytometry) or PCR (consensus primers) were eligible for inclusion in the study. Most patients had received fludarabine in combination with cyclophosphamide and rituximab. Alemtuzumab was started a minimum of 3 weeks after the end of chemotherapy at a dosage of 10 mg three times per week for 4 weeks. If disease remained at 8 weeks, patients received another 4 weeks of alemtuzumab at a higher dosage of 30 mg three times per week. After analysis of the first 24 patients, subsequent patients were started directly at 30 mg three times per week in an effort to increase the response. Alemtuzumab improved the overall response rate in 46% of patients (39% receiving the 10 mg dose level versus 56% receiving the 30 mg dose level); residual bone marrow disease was eradicated more frequently than lymph node disease. The main reason for failure to respond to treatment was cited as the presence of adenopathy. Overall, molecular disease remissions were achieved in 38% of patients and preliminary data suggested that this might indicate a longer duration of disease remission (Figure 1).

Table 1: Improvement in quality of response with alemtuzumab consolidation therapy following fludarabine-based induction in patients with CLL.

Reference	Fludarabine induction		Alemtuzumab consolidation		
	n	Response	n	Schedule	Response
13	34	12 CR, 7 nPR, 15 PR	34	3x10 mg SC >8 wk	27 CR, 4 nPR, 3 PR
14	5	1 CR, 3 PR, 1 SD	5	3x30 mg IV 4-8 wk	4 CR, 1 PR
15	41	3 CR, 17 nPR, 21 PR, 2 CR	24/17	3x10 mg IV 4 wk 3x30 mg IV 4 wk	9/23 (39%) 9/16 (56%)
16	56	29 PR, 10 PD, 11 SD	36	3x30 mg IV 6wk	15 CR, 18 PR
17*	11/10	1 CR, 10 PR/2 CR, 2 nPR, 3 PR, 3 PD	11	3x30 mg IV 12wk	3 CR, 8 PR

*Randomised trial (alemtuzumab consolidation vs. observation); CR = complete response; IV = intravenous; nPR = nodal partial response; PR = partial response; SC = subcutaneous; SD = stable disease.

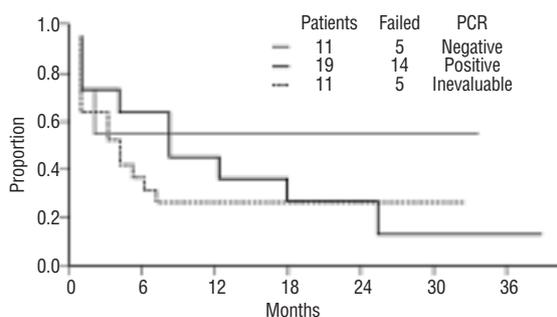


Figure 1: Time to disease progression by polymerase chain reaction (PCR) status after treatment with alemtuzumab¹⁵ This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc, from O'Brien S, *et al.* Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. *Cancer* 2003;98:2657-63. Copyright ©2003 American Cancer Society.

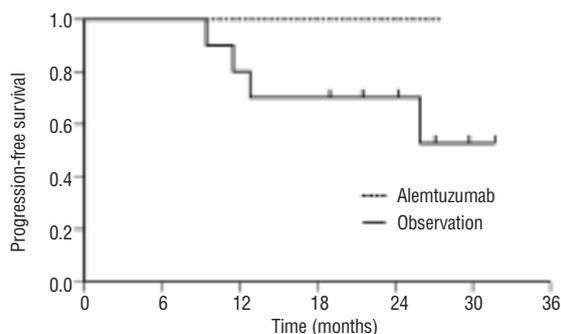


Figure 2: Progression-free survival (PFS) in CLL patients receiving alemtuzumab consolidation treatment (n=11; dashed line) and no further consolidation treatment/observation (n=10; solid line) after initial fludarabine-based chemotherapy ($p=0.036$).¹⁷ Reprinted by permission from Macmillan Publishers Ltd: *Leukemia* 2004;18:1093-101. Copyright ©2004.

A randomized phase III trial initiated by the German CLL Study Group (GCLLSG) confirmed the ability of alemtuzumab to eradicate MRD when administered as consolidation therapy.¹⁷ Patients in PR or CR following chemotherapy with fludarabine or fludarabine + cyclophosphamide were randomized to receive consolidation therapy with IV alemtuzumab 30 mg three times per week for up to 12 weeks or no further treatment. Of 21 evaluable patients, 11 (1 CR, 1 nPR, 9 PR) were randomized to active treatment. The data demonstrated that consolidation therapy with alemtuzumab induced pronounced reductions in MRD along with clinical remissions in CLL patients. All treated patients showed pronounced MRD reduction to a median level of 5×10^{-5} from a median level of 2.2×10^{-3} achieved following first-line treatment. MRD levels achieved with alemtuzumab were similar to those seen following autologous stem cell transplantation: during molecular follow-up, the median MRD level remained below 1×10^{-4} for about one year.¹⁸ At a median follow-up of 21.4 months from start of initial treatment, patients receiving alemtuzumab achieved a significantly longer progression-free survival

(PFS) compared with the control group (no progression versus mean 24.7 months; $p=0.036$) [Figure 2]. After a median follow-up of almost 3 years, only one relapse occurred in the alemtuzumab consolidation group compared to 7 (of 10) relapses in the observation group. Median PFS was still significantly shorter in the control group versus the treatment group ($p=0.04$).¹⁸

Due to the occurrence of severe acute infections in 7 patients, the GCLLSG study was ended at an earlier stage than planned; this may have been due, in part, to the short time interval between initiation of alemtuzumab and the last dose of fludarabine (<3 months; median 67 days) which may not have been sufficient to allow recovery from myelosuppression. However, the addition of alemtuzumab as a consolidation regimen following remission induction by fludarabine or fludarabine + cyclophosphamide was judged to have been highly effective and led to sustained MRD reduction, which translated into a significantly improved clinical outcome.¹⁸ The encouraging molecular responses noted in this study have led the GCLLSG to initiate a new phase I/II alemtuzumab dose-finding study in CLL

patients after induction of clinical remission by fludarabine-based therapy.

A small-scale Italian study of 9 CLL patients (median age 55 years) remaining MRD-positive after induction chemotherapy has confirmed the feasibility of peripheral blood stem cell (PBSC) collection following consolidation therapy with subcutaneous alemtuzumab.¹⁹ Of particular note, the use of alemtuzumab allowed a stem cell harvest that was uncontaminated by CD5/CD19 double-positive CLL cells. Furthermore, subcutaneous administration of alemtuzumab provided comparable efficacy to IV administration with regard to elimination of MRD, and was only associated with mild adverse skin reactions. The incidence of infection was generally low in patients who received alemtuzumab consolidation therapy, with the most common infections reported being reactivation of cytomegalovirus (CMV). Although the majority of such infections were resolved with ganciclovir, weekly PCR screening of patients receiving alemtuzumab consolidation therapy was recommended in order to detect CMV reactivation. A longer interval between induction therapy and alemtuzumab consolidation therapy also

appears to improve safety by allowing more time for recovery from myelosuppression, thereby reducing the risk of serious infections.

The combined ability of first-line fludarabine therapy followed by alemtuzumab consolidation to successfully purge residual cells from blood and bone marrow allows a high-quality CD34⁺ harvest, thereby preventing the transplantation of residual leukemic cells.¹⁰ This practice provides support for the approach of treating and greatly improving the prospects of relatively young patients with CLL.

The eradication of bone marrow MRD with subcutaneous alemtuzumab has also been investigated in a phase II study of patients with CLL who responded to fludarabine treatment (n=34).¹³ Patients received alemtuzumab consolidation in an effort to improve the quality of their response to fludarabine-based induction therapy. In this study, the feasibility of subsequent PBSC collection and transplantation, as well as tolerability were assessed. Patients aged <65 years who had a CR to fludarabine-based induction therapy received alemtuzumab 10 mg subcutaneously three times per week for 6 weeks. PBSCs were col-

Table 2: Ongoing European and US trials of alemtuzumab consolidation therapy in patients with CLL.

Country/trial	Schedule
Italy	Flu+Cyc (po) → PR followed by alemtuzumab consolidation (3x10 mg/wk SC) [first-line CLL]
Italy	Flu+Cyc followed by alemtuzumab consolidation (3x15 mg/wk 4 wk then 15 mg/2 wk 6 mth SC) [≥ second-line CLL]
France	Flu+Cyc (po) followed by alemtuzumab SC consolidation [first-line CLL]
Germany (CLL21)	Flu, Flu+Cyc or Flu+Cyc+Ritux → CR/PR followed by alemtuzumab IV/SC consolidation [second-line CLL]
USA (CALGB 10101)	Flu+Ritux followed by alemtuzumab consolidation
USA (ECOG 2903)	Pen+Cyc+Ritux followed by alemtuzumab consolidation
USA (CRC)	Chemotherapy followed by alemtuzumab consolidation
USA	Flu+Cyc followed by alemtuzumab consolidation

CALGB = Cancer and Leukemia Group B; CR = complete response; CRC = Chemotherapy followed by Campath® Consolidation; Cyc = cyclophosphamide; ECOG = Eastern Cooperative Oncology Group; Flu = fludarabine; IV = intravenous; Mit = mitoxantrone; mth = month; Pen = pentostatin; po = oral; PR = partial response; Ritux = rituximab; SC = subcutaneous; wk = week.

lected following mobilization with cytarabine and granulocyte colony-stimulating factor. Following alemtuzumab consolidation, the CR rate of 35% achieved with fludarabine induction therapy increased to 79.4%; 19 patients (56%) achieved MRD-negativity. Common adverse events included injection-site reactions and fever, as per previous studies. Although CMV reactivation was reported in 18 patients, all were successfully treated with oral ganciclovir. PBSC collection was successful in 24 (92%) of 26 patients, and 18 patients underwent autologous PBSC transplantation. Thus, the effectiveness and good tolerability with subcutaneous alemtuzumab as consolidation therapy in patients with CLL who responded to fludarabine-based induction therapy was confirmed. In addition, PBSC transplantation following alemtuzumab consolidation appeared feasible.

Ongoing trials

A further 15 studies of alemtuzumab consolidation therapy in CLL are either ongoing or planned in the European Union (8 studies) and the United States (7 studies). Ongoing studies in the two regions are summarized in Table 2. The trials include patients with both first-line and second-line CLL and the results of these trials are awaited with interest.

Conclusions

Consolidation therapy with alemtuzumab after fludarabine or fludarabine-based chemotherapy is effective in a substantial proportion of patients with CLL. This therapeutic approach provides an improvement in the quality of clinical responses, increases progression-free survival, eradicates MRD, and achieves molecular remissions in a high num-

ber of patients. Although alemtuzumab consolidation is not yet a treatment standard in CLL, this approach contributes to a change in the treatment goal from palliation to cure. Consolidation therapy with alemtuzumab has, however, been associated with a risk of infectious events. Such events were particularly observed when alemtuzumab was administered within a short-time interval following induction therapy. A longer time interval of 3 to 6 months between induction and alemtuzumab consolidation therapy may improve safety by allowing time for recovery from myelosuppression.

Presently ongoing and future trials will need to answer open questions regarding the optimal timing, schedule and dose of alemtuzumab consolidation therapy.

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