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Long-term follow-up of symptomatic patients with lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia treated with the anti-CD52 monoclonal antibody alemtuzumab

Steven P. Treon¹, Jacob D. Soumerai¹, Zachary R. Hunter¹, Christopher J. Patterson¹, Leukothea Ioakimidis¹, Brad Kahl², and Michael Boxer³.

¹Dana-Farber Cancer Institute, Harvard Medical School, Boston MA, USA;

²Carbone Cancer Center, University of Wisconsin, Madison, WI; ³Arizona Oncology Associates, University of Arizona, Tucson AZ.

Corresponding author:

Steven P. Treon M.D., M.A., Ph.D.

Bing Center for Waldenström's Macroglobulinemia

Dana-Farber Cancer Institute

Harvard Medical School

M547, 44 Binney Street

Boston MA 02115 USA

Tel: (617) 632-2681

Fax: (617) 632-4862

Email: steven_treon@dfci.harvard.edu

ABSTRACT

CD52 is expressed on lymphoplasmacytic cells in lymphoplasmacytic lymphoma (LPL), including IgM secreting Waldenstrom's Macroglobulinemia. We examined the activity of alemtuzumab in 28 symptomatic LPL (27 IgM; 1 IgA) patients. The median prior therapies for these patients was 2 (range 0-5), and 43% had refractory disease. Patients received alemtuzumab intravenously at 30 mg three times weekly for up to 12 weeks, after test dosing, and received hydrocortisone, acyclovir, and bactrim or equivalent prophylaxis. Responses: CR (n=1); PR (n=9); MR (n=11) for an overall and major response rate of 75% and 36%, respectively. Median serum Ig decreased from 3,510 to 1,460 mg/dL; $p < 0.001$ at best response. With a median follow-up of 64 months, the median time to progression was 14.5 months. Hematological and infectious complications, including CMV reactivation were more common in previously treated patients and indirectly associated with 3 deaths. Long term follow-up revealed late-onset idiopathic thrombocytopenia (ITP) in 4 patients at a median of 13.6 months following therapy, and contributed to one death. Alemtuzumab is active in patients with LPL, though short and long-term toxicities need to be carefully weighed against other available treatment options. Late ITP is a newly recognized complication of alemtuzumab in this patient population. This study is registered at www.clinicaltrials.gov as NCT00142181.

INTRODUCTION

Lymphoplasmacytic lymphoma (LPL) is a B-cell disorder characterized by bone marrow infiltration with lymphoplasmacytic cells and an immunoglobulin monoclonal gammopathy.^{1,2} Inclusive in the diagnosis of LPL is Waldenström macroglobulinemia (WM), which is characterized by secretion of IgM, to which particular morbidities are more common including hyperviscosity syndrome, cryoglobulinemia, cold agglutininemia, and sensory neuropathy.^{3,4} Despite advances in therapy, LPL remains incurable, and novel therapeutic agents are urgently needed.

Monoclonal antibody therapy, particularly rituximab, has been an important mainstay in the therapy of symptomatic patients with WM, with overall response rates (ORR) of 25% to 45%, and median durations of response of 8 to 29 months.⁵⁻⁸ No complete responses were observed in these studies. Ofatumumab is a novel CD20 directed antibody, which was recently evaluated as monotherapy in symptomatic WM patients, with an ORR of 43%.⁹ Both rituximab and ofatumumab can produce an IgM flare, prompting hyperviscosity symptoms and/or exacerbation of IgM related morbidities in WM patients.^{3,4,9-11}

In view of these considerations, we and others have sought to develop other targeted therapies for LPL/WM patients. Alemtuzumab is a fully humanized human IgG1 monoclonal antibody which targets CD52, with established efficacy in the treatment of other lymphomas.^{12,13} CD52 is widely expressed on BM lymphoplasmacytic cells in WM.¹⁴⁻¹⁶ Importantly, CD52 is selectively expressed on WM patient mast cells (MC) which are found in excess numbers in their bone marrows, and support the growth and survival of WM cells through CD40 ligand stimulation.^{17,18} Alemtuzumab induces antibody dependent cell mediated cytotoxicity (ADCC) against BM mast cells from WM patients.¹⁹ Given these findings, we performed a prospective phase II study of alemtuzumab in symptomatic patients with LPL/WM, and present the long term outcome of these studies.

PATIENTS AND METHODS

Eligibility

Symptomatic patients with a clinicopathologic diagnosis of lymphoplasmacytic lymphoma (LPL, including patients with IgG, IgA and IgM paraproteins, i.e. Waldenstrom's macroglobulinemia), who were naive to alemtuzumab, who had CD52-positive disease as determined by previous bone marrow immunohistochemistry or flow cytometry, and who required therapy based on consensus guidelines were eligible for this study.²⁰ A baseline platelet count of more than or equal to 25,000/ μ L, an absolute neutrophil count of more than or equal to 500/ μ L, a serum creatinine of less than 2.5 mg/dL (unless nephropathy was attributable to their WM), a serum total bilirubin and serum glutamicoxalacetic transaminase of less than 2.5 times the upper limit of normal, and an Eastern Cooperative Oncology Group performance status of 0 to 2 were required for entry. No other monoclonal antibody therapy within 3 months of study entry was permitted. No chemotherapy, steroid therapy, or radiation therapy within 30 days of study entry was permitted. Patients who were pregnant or lactating, had serious comorbid disease, had any uncontrolled bacterial, fungal, or viral infection, or had an active second malignancy were not eligible. All men and women of reproductive potential were required to agree to use an acceptable method

of birth control before and during treatment as well as for 6 months after completion of study treatment.

Treatment

Intended therapy consisted of 3 test doses of alemtuzumab initiated using a gradual dose escalation schedule over one week (3mg, 10mg, 30mg), followed by 36 additional treatment phase infusions of alemtuzumab at the 30mg dose, given IV three times per week over 12 weeks. Patients received prior to their alemtuzumab infusions one liter of normal saline, diphenhydramine 50 mg IV, acetaminophen 650 mg by mouth, as well as hydrocortisone 100-200 mg IV and cimetidine 300 mg IV (if they reacted to a previous alemtuzumab infusion) to prevent infusion related reactions. Famciclovir 250 mg twice a day or equivalent, and sulfamethoxazole and trimethoprim (double strength) twice a day on three days per week was given for herpes zoster and PCP prophylaxis, respectively, for the duration of alemtuzumab treatment plus 3 months. Dapsone was permitted for patients who had sulfur allergy in lieu of sulfamethoxazole and trimethoprim. Baseline CMV viral loads were obtained on all patients, and treatment was halted and gancyclovir begun in patients who demonstrated CMV reactivation.

Patients were assessed for response following the first 18 treatment phase infusions, and if stable disease or better were eligible to continue treatment. Dose or schedule modification was permitted as follows: Alemtuzumab was held for ≥ 2 non-hematologic and/or grade ≥ 3 hematologic toxicities. For the first occurrence, alemtuzumab was restarted at 30 mg when toxicities resolved to $<$ grade 2 for non-hematologic or $<$ grade 3 for hematologic toxicities, respectively. For the second occurrence, alemtuzumab was restarted at 10 mg. For the third occurrence, alemtuzumab was permanently discontinued. In the event that alemtuzumab was discontinued for greater than 7 days, alemtuzumab was restarted using the test dose escalation schedule noted above.

Study design

A Simon 2-stage design was used. Using 90% power and alpha set at 0.05, 13 patients were to be included in the first stage of the 2-stage design to test the null hypothesis that the probability of response is less than or equal to 20% versus the alternative that probability of response is more than or equal to 45%. For the first stage, after alemtuzumab was administered to 13 patients, the study would have been terminated if 3 or fewer patients respond. If 4 or more patients responded in the first stage of the trial, an additional 14 patients were to be enrolled and treated during stage II. If,

after study completion, the total number of responding patients was greater than 8, then alemtuzumab would be deemed truly effective and the null hypothesis that alemtuzumab produces a response rate less than 20% would be rejected.

Response determination

A baseline evaluation was obtained for enrollment within 30 days before initiation of therapy. Patients underwent restaging studies at 6 and 13 weeks and thereafter every 6 months until progression of disease. As part of their response evaluation, all patients underwent history and physical examination; laboratory studies consisting of a complete blood count and differential, quantitative total serum immunoglobulins and serum immunoelectrophoresis. A bone marrow biopsy and aspiration were only performed following treatment to confirm a complete response. Response determinations were made using modified consensus panel criteria from the Third International Workshop on WM,^{21,22} and response rates were determined on an intent to treat basis. Patients with relapsed disease were defined as those subjects who demonstrated progressive disease after previous treatment response, whereas patients with refractory disease were defined as non-responders to their previous therapy. Median time to progression was calculated from the start of therapy using the Kaplan Meier

method using consensus criteria for disease progression.²¹ Primary endpoints for this study were best categorical response attainment, determination of median progression free survival (PFS), and toxicity. Changes in serum IgM levels and blood counts following alemtuzumab therapy were also assessed at best response. The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board. Informed consent was obtained in accordance with the Declaration of Helsinki.

Analysis of peripheral blood effector cells

Serial changes in the absolute levels of peripheral blood effector cells were performed as previously described.²³

Statistical analysis

Comparison of pretreatment and posttreatment parameters was performed using a 2-tailed Student t test on Microsoft Excel software. A p-value less than or equal to 0.05 was deemed to be significant for the aforementioned studies.

RESULTS

Patient and disease characteristics

The clinical features of the 28 patients enrolled in this study are summarized in Table 1. Twenty-seven of the 28 patients had WM. One patient had an IgA-secreting lymphoplasmacytic lymphoma. Of the 28 patients enrolled on study, 23 were previously treated. Eleven (36%) and 12 (43%) of previously treated patients had relapsed or refractory disease, respectively. Among previously treated patients, the median number of prior therapies was 2 (range 1-5). The median number of alemtuzumab infusions received was 36 (7-36), with 15 (53.6%) patients completing the full course of 36 treatment infusions. Two patients did not return for response assessment and therefore were not evaluable for response.

Clinical response to therapy

The individual changes in serum IgM levels at best response for all evaluable patients are shown in Figure 1. Median serum IgM levels for all evaluable patients with IgM-secreting LPL declined from 3,510 mg/dL (range, 622 to 8,620 mg/dL) to 1,460 mg/dL (range, 105 to 8,750 mg/dL) at best response ($P < 0.001$). IgA declined from 1,210 to 529 at best response for the one

patient with IgA LPL. On an intent-to-treat basis, the best overall response rate was 75%, with 10 (36%) and 11 (39%) patients achieving a major and a minor response, respectively. Seventeen of the 21 responders achieved at least a minor response by 13 weeks. Among major responders, one WM patient who received alemtuzumab as primary therapy achieved a complete response. The best ORR and major response rate for untreated patients was 100% and 80%, respectively, versus 76% ($p=0.54$) and 29% ($p=0.054$) for previously treated patients, respectively. No differences in response rates (overall or major) were observed among previously treated patients with relapsed versus refractory disease ($p=1.0$ and 0.63 , respectively). Best overall (80% vs. 83.3%) and major (40% vs. 33.3%) responses did not differ when all patients were stratified by baseline serum IgM level, i.e. $<6,000$ vs. $\geq 6,000$ mg/dL, respectively ($p=1.0$ for both response determinations). For 5 patients with adenopathy ($n=5$) or splenomegaly ($n=1$), no change ($n=3$), improvement ($n=1$), and resolution ($n=1$) occurred following alemtuzumab therapy. For responding patients, the median time to best response was 7.4 months (range, 1.3 to 54.4 months).

Time to Progression

With a median follow-up of 64 (range 1.3-89.8 months), 14 of 21 (66.7%) responders have progressed. As shown in Figure 2, the median time to

progression (TTP) for all 28 patients was 14.5 (range, 1.3 to 65.4 months), and for responding patients was 16.8 (range, 1.3 to 65.4 months).

Toxicities

Toxicities encountered were mainly hematological and infectious, and contributed indirectly to 3 study deaths, while on therapy, and possibly to another death due to late emergence of immune thrombocytopenia. Encountered toxicities led to truncation of intended therapy in 13 patients due to: myelosuppression (n=6) including pancytopenia (n=3), neutropenia (n=2), and thrombocytopenia (n=1); CMV reactivation (n=5); esophageal candidiasis (n=1); and lack of prompt response in a patient who presented with hyperviscosity (n=1). Grade ≥ 2 toxicities are depicted in Table 2. Grade 3 or higher toxicities were more pronounced in previously treated (17/23; 73.9%) versus untreated (1/5; 20.0%) patients (p=0.041), with rash constituting the only grade 3 toxicity encountered in an untreated patient which resolved with a short course of systemic steroid therapy.

Grade ≥ 3 hematological toxicities included neutropenia, thrombocytopenia, and anemia which occurred in 53.6%, 25.0%, and 10.7% of patients, respectively. One patient who relapsed after attaining a CR with CHOP-rituximab developed autoimmune hemolytic anemia 4 weeks after

discontinuation of alemtuzumab which remitted after a short course of prednisone. Another patient with acquired Von Willebrand's disease (aVWD), whose disease was refractory to rituximab, thalidomide, and bortezomib developed grade 3 thrombocytopenia while on alemtuzumab therapy, which possibly contributed to a fatal hemorrhagic event suspected on the basis of the patient's underlying aVWD.

CMV reactivation was the most common infectious event which occurred in 5/28 (17.8%) prompting discontinuation of alemtuzumab, and was symptomatic in 4 of these 5 (80%) patients. Two patients who experienced CMV reactivation developed pancytopenia following institution of anti-viral (ganciclovir, valganciclovir) therapy. Both succumbed to infectious complications unrelated to CMV, including one patient who developed coagulase-negative staphylococcal endocarditis leading to a fatal embolic stroke, and another patient with bronchoalveolar lavage (BAL) culture negative pneumonia which progressed to fatal acute respiratory distress syndrome. In both cases, prolonged neutropenia associated with anti-CMV therapy were deemed to have contributed to these events.

Late-onset alemtuzumab related immune thrombocytopenia

With a median follow-up of 64.0 months, we observed new onset immune

thrombocytopenia in 4 (14.3%) patients, which occurred at a median of 12.9 (range 3.6 to 22.9 months) following completion of therapy. All 4 of these patients had WM, and received 36 treatment infusions of alemtuzumab, and no other interim therapy until time of the ITP diagnosis. The median platelet count at the time of ITP diagnosis was 12,000 (range 1,000-31,000/mm³). The diagnosis of ITP was confirmed in all cases by a bone marrow biopsy which demonstrated adequate megakaryocytes, and no other attributable causes, including WM or iatrogenic factors. One patient whose ITP was refractory to systemic treatment and splenectomy succumbed to an intracranial hemorrhage in the setting of severe thrombocytopenia 16 months following diagnosis of ITP. A second patient with refractory ITP to systemic therapy and splenectomy succumbed to rapidly metastasizing colon cancer. A third patient whose ITP responded to rituximab and steroids, remains steroid dependent > 55.4 and >30.8 months following alemtuzumab therapy, and development of ITP, respectively. A fourth patient who developed post-alemtuzumab related ITP, achieved a complete response to treatment with steroids and rituximab.

Impact of alemtuzumab on peripheral blood immune cells and immunoglobulin levels.

Median absolute peripheral blood cell levels for CD4⁺, CD8⁺, CD16⁺56⁺, CD19⁺ and monocytic cells (cells/mm³) are shown in Figure 3, and did not differ between previously untreated and treated patients (data not shown). As shown in Figure 3, significant decreases in CD4⁺ (p<0.0001), CD8⁺ (p<0.0001), CD16⁺56⁺ (p≤0.02), CD19⁺ (p<0.0001) and monocytic cells (p<0.0001) occurred during the active treatment period, with persistent suppression of CD4⁺, CD8⁺, CD19⁺ and monocytic cells, but not CD16⁺56⁺ noted throughout the 2 year follow-up period. During the 2-year follow-up period, no significant changes in serum IgA and IgG levels were observed (data not shown).

DISCUSSION

We set out to define in these studies the efficacy and safety of alemtuzumab in a multicenter phase II study, given the wide expression of CD52 on LPL cells. The strength of this study is the prospective design with a relatively large number of patients with LPL, almost all of whom were subjects with WM, as well as the long-term median follow-up period of 64 months which was essential in identifying long-term treatment related complications. The results of this study have important implications to the care of patients with LPL. From a response perspective, the results clearly identify alemtuzumab as an active agent in LPL with an overall response rate of 75%, inclusive of 36% of patients who achieved a major response (i.e. $\geq 50\%$ decrease in disease burden). Responses were observed in both symptomatic patients with untreated as well as previously treated disease, though major responses were higher in untreated versus previously treated patients (80% versus 29%, $p=0.054$).

A similar finding of higher response activity in untreated versus previously treated patients has been observed in CLL patients, and may be related to depletion or functional inactivation of effector cells by previous chemotherapy.^{24,25} High response rates were observed in this study in patients with relapsed as well as refractory disease, and were not influenced

by the baseline level of serum IgM which has been reported to be an important determinant for response in WM patients receiving rituximab antibody.^{7,8} High rates of response with the use of alemtuzumab were also observed by Owen et al²⁶ who reported their preliminary experience in a small series of heavily pretreated WM patients. The median number of prior therapies in this series was 4, and similar to this study patients received up to 12 weeks of therapy (at 30 mg IV three times weekly) following initial dose escalation. Among the 7 patients treated with alemtuzumab, 5 achieved a partial response and one a complete response.

In comparison to previous experiences with rituximab in symptomatic WM patients, our studies and those by Owen²⁶ suggest higher overall activity with alemtuzumab (i.e. 75-85% vs. 25-45%). These differences are unlikely to be dose related since a smaller dose of alemtuzumab was administered during the 12 week treatment inclusive of test doses, i.e. 1123 mg/m² versus 1500 mg/m² with standard and 3000 mg/m² with extended course rituximab, respectively. While a number of antibody specific considerations could account for these differences, the possible elimination of CD52⁺ supportive microenvironmental cells such as mast cells, monocytes or T-cells could account for the more robust activity observed with alemtuzumab in comparison to rituximab.^{18-20,27,28} Also notable in the present study was the time to progression of 15.6 months, which is on par if not better than that

reported with other active single agents in symptomatic LPL including nucleoside analogues, rituximab and bortezomib.^{3,4}

While the activity of alemtuzumab in this study of symptomatic LPL patients was notable, short and long-term adverse events were remarkable as well. Neutropenia and thrombocytopenia were particularly impressive, with 53.6% and 25.0% of patients experiencing grade ≥ 3 events, respectively, during active therapy. While previous studies negated CD52 expression on neutrophils, a recent study showed CD52 is in fact expressed on neutrophils and alemtuzumab leads to their direct complement mediated lysis *in vitro*.²⁹ As such, the presence of neutropenia following alemtuzumab therapy is explainable in this patient population. However, the production of thrombocytopenia by alemtuzumab is at odds with megakaryocytes not being CD52 expressive, as well as the finding that megakaryopoiesis is actually enhanced in colony forming assays by alemtuzumab.³⁰ The precise mechanism for this finding remains speculative, but may involve depletion of CD52 expressing T-cells which autoregulate megakaryopoiesis. In addition to myelosuppression which occurred during treatment, our studies also identified ITP as a late consequence of alemtuzumab therapy. Four cases of late alemtuzumab related ITP were identified, which was related to one death. In addition, one case of autoimmune hemolytic anemia was observed. A previous report identified autoimmune thrombocytopenia after treatment

with alemtuzumab in a patient with CLL.³¹ One potential unifying hypothesis for these observations is the selection phosphatidylinositolglycan (PIG)-deficient cells, which has been reported following alemtuzumab therapy and could result in the selection of complement defense antigen deficient cells lacking CD55 and CD59 thereby rendering these cells susceptible to complement attack.³² It is worth noting that all grade ≥ 3 hematological events, as well as late-ITP events occurred in previously treated individuals thereby raising the possibility that prior drug therapy may have contributed to alemtuzumab related hematological complications.

Routine surveillance permitted the identification of CMV reactivation occurred in 5 (18%) patients, all of whom were previously treated. CMV reactivation was not predicted by baseline effector cell levels, including CD4 counts (data not shown). The rate of CMV reactivation in this study was in line with that previously reported with the use of alemtuzumab as salvage therapy in CLL patients (20%),³³ but lower than that reported by Owen et al²⁶ in more heavily pretreated patients (43%). Two patients who developed CMV reactivation succumbed, though the etiology of their deaths was related to CMV-directed therapy which produced prolonged neutropenia and contributed to fatal infections. The use of valgancyclovir for prophylaxis of CMV reactivation at lower doses than those used for therapeutic intent as reported by O'Brien et al³⁴, as well as advances in less myelosuppressive

CMV-directed therapy may ultimately permit for more safe administration of alemtuzumab to patients. While not observed by us in a less pre-treated population of WM patients, disseminated aspergillus and mycobacterial infections contributed to 2 deaths (out of 7 patients) in the series by Owen et al²⁶ in heavily pretreated WM patients who received alemtuzumab.

In conclusion, alemtuzumab is an active agent in patients with LPL, though short and long-term toxicities need to be carefully weighed against other available treatment options. Late ITP is a newly recognized complication of alemtuzumab in this patient population.

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AUTHORSHIP

SPT designed the trial, recruited and treated patients, and analyzed the data. JDS, ZRH, CJP, and LI served as clinical research coordinators for this trial, and collected, analyzed data. BK and MB were site principal investigators, and recruited patients, collected data, and reviewed study outcome. SPT and JDS wrote the manuscript. Berlex Pharmaceuticals provided research funding, and drug replacement in support of these studies. Authors have no other relevant disclosures to this study.

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| | Median | Range |
|---|---------------|--------------|
| Age, years | 59.5 | 33-75 |
| Male/Female | 18/10 | N/A |
| Previously treated | 23 (82.1%) | N/A |
| Median prior therapies | 2 | 0-5 |
| Bone marrow involvement, % | 30 | 5-90 |
| Adenopathy/Splenomegaly | 5 (17.9%) | N/A |
| Serum IgM, mg/dL | 3,510 | 622-12,000 |
| B₂M, mg/L | 3.1 | 1.3-6.9 |
| Hematocrit, % | 35.0 | 24.4-42.8 |
| Platelets, 1000/μL | 232 | 72 -486 |
| Leukocytes, 1000,μL | 5.45 | 2 -13 |

Table 1: Baseline characteristics for 28 LPL patients enrolled on study.

| | ≤ Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|-------------------------------|------------------|----------------|----------------|----------------|
| Leukopenia | 23 (82.1%) | 7 (25.0%) | 9 (32.1%) | 0 (0%) |
| Neutropenia | 16 (57.1%) | 11 (39.3%) | 4 (14.3%) | 0 (0%) |
| Thrombocytopenia | 12 (42.9%) | 4 (14.3%) | 3 (10.7%) | 1 (3.6%) |
| Anemia | 12 (42.9%) | 3 (10.7%) | 0 (0%) | 0 (0%) |
| Infection | 11 (39.3%) | 3 (10.7%) | 2 (7.1%) | 2 (7.1%) |
| Fatigue | 5 (17.9%) | 2 (7.1%) | 0 (0%) | 0 (0%) |
| Rash | 4 (14.3%) | 3 (10.7%) | 0 (0%) | 0 (0%) |
| Dyspnea | 3 (10.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hyperglycemia | 3 (10.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Arthralgia | 3 (10.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Myalgia | 2 (7.1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nausea | 2 (7.1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Allergic Reaction | 2 (7.1%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Chest Pain | 2 (7.1%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Hyponatremia | 1 (3.6%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Transaminitis | 1 (3.6%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Abdominal Pain | 1 (3.6%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Constipation | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Edema | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Mucositis | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Back Pain | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Myasthenia | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Stomatitis | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Dyspepsia | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fever | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Deep Venous Thrombosis | 1 (3.6%) | 0 (0%) | 0 (0%) | 0 (0%) |

Table 2. Toxicities possibly, probably or definitely related to treatment in 28 LPL patients who underwent therapy with alemtuzumab.

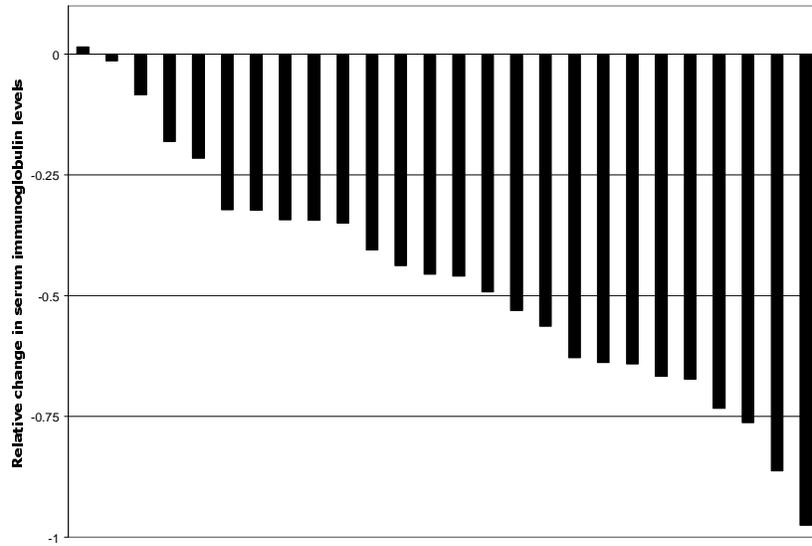


Figure 1. Relative changes in serum immunoglobulin levels for 26 evaluable LPL patients at best response following treatment with alemtuzumab.

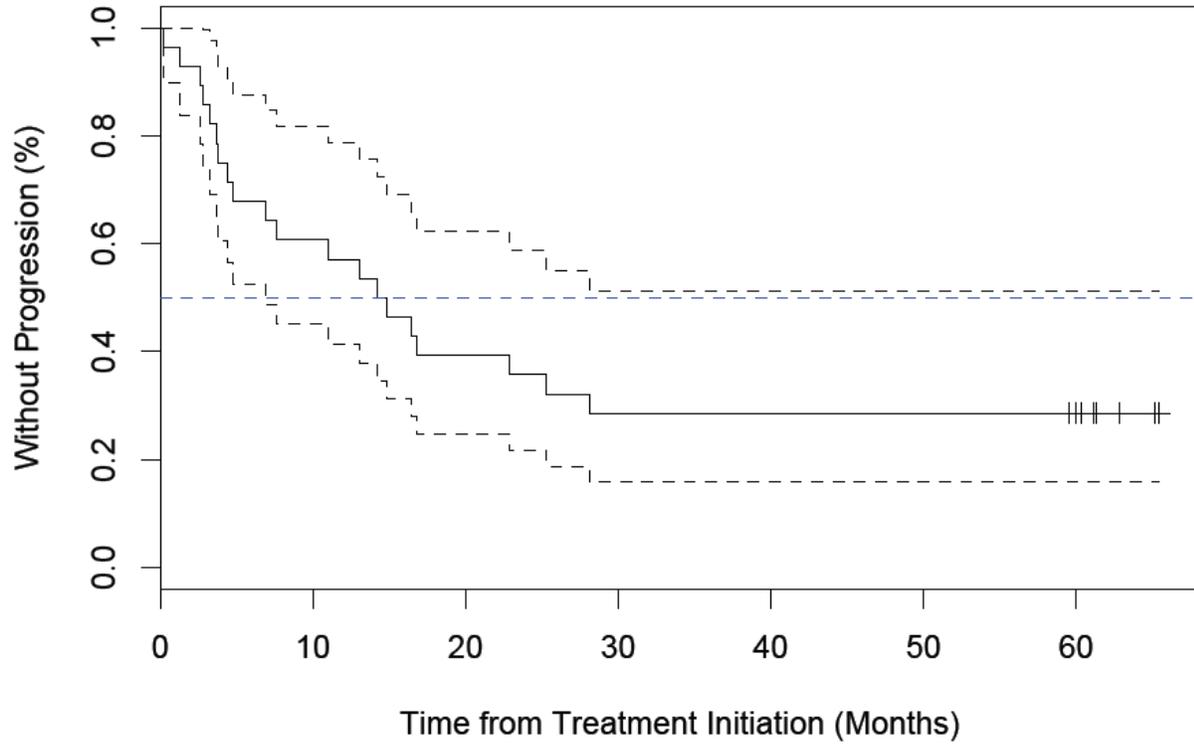


Figure 2. Time to progression for 28 LPL patients treated with alemtuzumab.

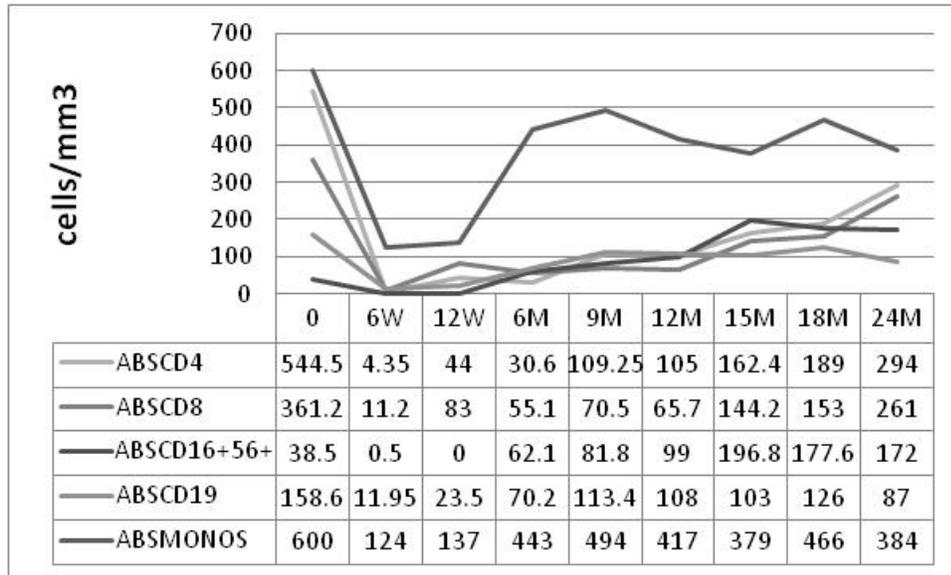


Figure 3. Median absolute peripheral blood CD4⁺, CD8⁺, CD16⁺56⁺, CD19⁺ and monocytic cell levels (cells/mm³) at baseline (0), 6 and 12 weeks (6W, 12W), and 6 to 24 months (6M to 24M) following alemtuzumab therapy. Patients evaluated at each time point were as follows: 0 (n=26); 6W (n=18); 12W (n=22); 6M (n=16); 9M (n=17); 12M (n=13); 15M (n=10); 18M (n=11); 24M (n=8).