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A Phase II Randomized Trial Comparing Standard and Low Dose Rituximab Combined with Alemtuzumab as Initial Treatment of Progressive Chronic Lymphocytic Leukemia in Older Patients: A Trial of the ECOG-ACRIN Cancer Research Group (E1908)

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Abstract

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) patients requiring initial therapy are often older and frailer and unsuitable candidates for standard chemoimmunotherapy regimens. Shorter duration combination monoclonal antibody (mAb) therapy using alemtuzumab and rituximab has been shown to be effective and tolerable treatment for CLL. Standard dose anti-CD20 mAb therapy causes loss of CD20 expression by surviving CLL cells, which can be minimized by decreasing the mAb dose. We report a randomized phase II clinical trial enrolling

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older (≥65 years) patients (median age 76 years, n=31) with treatment naïve progressive CLL. Patients received 8–12 weeks of standard subcutaneous alemtuzumab with either intravenous standard (375 mg/m^2 weekly)(n=16) or low dose (20 mg/m^2 3x week)(n=15) rituximab. This study was closed before full accrual because the manufacturer withdrew alemtuzumab for treatment of CLL. The overall response rate was 90% with an 45% complete response rate, median progression free survival of 17.9 months and no significant differences in outcome between the low and standard dose rituximab arms. The major toxicities were cytopenia and infection with one treatment fatality caused by progressive multifocal leukoencephalopathy but no other opportunistic infections. Combination mAb therapy was effective and tolerable treatment for older and frailer patients with progressive CLL, achieving a high rate of complete remissions. These data support the role of mAb in therapy for less fit CLL patients and the further study of low dose higher frequency anti-CD20 mAb therapy as a potentially more effective use of anti-CD20 mAb in the treatment of CLL.

Keywords

chronic lymphocytic leukemia; small lymphocytic lymphoma; CLL; elderly; therapy; low dose rituximab; alemtuzumab; monoclonal antibodies

Introduction

The median age at diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is 71 years [1]. Approximately 90% of CLL patients do not require treatment at diagnosis and by the time that therapy is indicated, many are elderly and frail and thus not suitable candidates for standard chemoimmunotherapy regimens [2, 3]. There is thus a need to develop effective and less toxic therapy options for this patient population.

Alemtuzumab and rituximab are unconjugated monoclonal antibodies (mAb) that target discrete CLL membrane antigens and utilize the innate immune system to kill CLL cells [4, 5]. Combination therapy with alemtuzumab and rituximab achieved high response rates in phase II studies [6–10]. Although these response rates are higher than those previously reported for monotherapy with either mAb [6–11], there are no reported randomized studies showing conclusively that the addition of rituximab to alemtuzumab therapy in CLL patients improves outcome. However, the alemtuzumab and rituximab regimen was well tolerated and thus considered an option for non-chemotherapy initial treatment of elderly patients with progressive CLL.

There are limited data on the optimal dosing regimen for rituximab in CLL. Previously published studies have shown that higher frequency low dose therapy can decrease the loss of CD20 expression by circulating CLL cells that occurs with standard dose rituximab therapy [12–14]. In this paper we report the results of one of the first clinical trials in CLL designed specifically for older CLL patients using a non-chemotherapy combination therapy that tested the utility of use of higher frequency low dose rituximab. Our study shows that short duration alemtuzumab and rituximab at both standard and low dose higher frequency administration can achieve a high remission and complete rate in this patient population.

These responses were achieved with acceptable rates of toxicity but were unfortunately not of sufficient duration to consider this a major therapeutic advance.

Methods

Patient Selection

This randomized two-arm phase II study was designed to evaluate the efficacy and toxicity of alemtuzumab and either standard or higher frequency low dose rituximab in older patients with treatment naïve progressive CLL. The study was conducted by the ECOG-ACRIN Cancer Research Group with participating Institutional Review Boards approval according to the principles of the Declaration of Helsinki and was registered with Clinicaltrials.gov (NCT01013961). The primary objective was to compare the rates of complete response (CR) and overall response rates (ORR) of patients treated with standard and modified dose of rituximab. The secondary objectives were to assess the toxicity of these regimens and to determine the rates of progression-free survival (PFS) and overall survival (OS).

All eligible and consenting patients were enrolled in the study. Eligibility required that patients had progressive treatment naïve CLL or its small lymphocytic lymphoma variant based on standard criteria [15, 16] without massive splenomegaly (> 6 cm below the costal margin in the left mid clavicular line) or lymphadenopathy > 5 cm on clinical examination. The initial eligibility criteria required that patients be ≥ 70 years old but this was modified to ≥65 years on April 25, 2012. Patients were required to have an ECOG performance status of 0–3, and adequate organ function defined as a serum creatinine < 2 x upper normal limit for treating institution (UNL), total bilirubin < 1.5 x UNL or direct bilirubin < 1.5 X UNL and AST < 3.0 x UNL unless due to CLL involvement of the liver. Exclusion criteria were New York Heart Association Class III-IV heart disease, recent myocardial infarction, uncontrolled infection, HIV infection, active hepatitis B infection, positive hepatitis C serology, active autoimmune cytopenia, other active primary malignancy requiring treatment or that limits survival to ≤ 2 years, recent major surgery, or continuous systemic corticosteroid therapy.

Therapy

Patients were randomized 1:1 to alemtuzumab and standard dose rituximab (arm A) or alemtuzumab and higher frequency low dose rituximab (arm B) using risk stratification based FISH analysis done at a central reference laboratory. Patients with 17p13 deletion or 11q22 deletion were considered high risk, those with 13q14 deletion as the sole detected abnormality were considered low risk and those with no detected abnormalities, trisomy 12, or other any other abnormality were considered intermediate risk. The first cycle of therapy was 33 days to facilitate alemtuzumab dose escalation and the second and third cycles were 28 days. Alemtuzumab therapy was administered subcutaneously with a dose escalation of 3 mg day 1 (Wednesday), 10 mg day 2, and 30 mg day 3 of cycle 1. In patients who tolerated dose escalation, the alemtuzumab therapy continued at 30 mg three times a week (Monday-Wednesday-Friday) starting on day 6 of cycle 1. Patients on arm A received rituximab 375 mg/m^2/week IV starting on day 8 of cycle 1 and continued weekly. Patients on arm B received rituximab 20 mg/m^2 IV Monday, Wednesday and Friday starting on day 6 of cycle

1. Planned therapy was a minimum of two cycles. Patients with a clinical complete response (CCR) after two cycles of therapy underwent a more comprehensive response evaluation (detailed below) and therapy was stopped if they had achieved a CR. Patients with responding disease who had not achieved a CR received one additional cycle of therapy.

All patients received Pneumocystis jiroveci and herpes virus prophylaxis during therapy and then for 6 months after the last dose of alemtuzumab. Monitoring for cytomegalovirus (CMV) reactivation by serum CMV DNA copy number polymerase chain reaction (PCR) assays was initiated prior to therapy and then done every week during treatment and then monthly for two months after completion of therapy. In asymptomatic patients with detectible CMV viremia the treatment regimen was continued and they were treated with oral valganciclovir for at least 2 weeks and until the CMV antigenemia was shown to have resolved by repeat serum CMV PCR assays done one week apart. Patients with CMV viremia and clinical manifestations of infection were treated for infection as appropriate and CLL therapy was held until full recovery.

Response Evaluation

Toxicity was evaluated using the NCI Common Toxicity Criteria version 4.0. Patients were evaluated for response with National Cancer Institute-Working Group (NCI-WG 1996) criteria and computerized tomography (CT) and bone marrow evaluations compatible with the International Workshop on CLL updated NCI-WG criteria (IWCLL 2008) [15, 17]. After two cycles of therapy all patients with a CCR underwent a CT scan of chest-abdomen-pelvis. Patients with no evidence of residual adenopathy or hepatosplenomegaly proceeded to a bone marrow study including immunohistochemical staining (IHC) for residual disease. All patients with a CR without any evidence of residual CLL on CT and IHC did not receive any further therapy and did not undergo any additional response evaluation. All patients completing three cycles of therapy who met criteria for at least a partial response (PR) had a CT scan of chest-abdomen-pelvis and a bone marrow study two months after completing therapy to assess response to therapy.

Statistical Methods

Patients were stratified by FISH analysis results into high, intermediate and low risk groups and then randomized 1:1 to arms A and B using permuted blocks with dynamic balancing on main institutions [18]. The primary aim of this study was to compare the rates of CR and ORR of patients treated with either standard or higher frequency low dose rituximab. We assumed a CR rate of 35% for patients receiving standard dose rituximab and targeted a 65% CR rate for patients receiving the higher frequency low dose rituximab. Based on these assumptions, accrual of 90 patients (80 eligible) randomized equally to the two arms had a 90% power to detect a 30% improvement in CR rate at a one-sided 0.1 significance level. The study was to be stopped if the CR rate of the modified dose group was lower than the standard dose group in the first 40 eligible patients. The study was also to be stopped if we observed 5 or more patients with a grade 4 or higher non-hematological adverse event related to treatment in the first 15 patients. OS was defined as the time from randomization to death from any cause. Patients still alive were censored at the date of last contact. PFS was defined as the time from entry onto study until CLL progression or death from any

cause without documented progression. Patients without progression were censored at the date of last disease assessment, unless death occurred within three months following the date they were last known to be progression free. Kaplan-Meier estimates [19] were used for event-time distributions. The response frequencies were computed using the maximum likelihood estimate (the observed proportion of responses). Confidence intervals for response frequencies were computed using the exact binomial distribution. Fisher's exact test was used to compare the response rates.

Results

E1908 opened to accrual on October 8, 2010 and closed on October 31, 2013. The study only enrolled 31 of the planned 90 patients and was closed early because of poor accrual. The decrease in the accrual rate was primarily caused by the withdrawal of alemtuzumab for the treatment of CLL by the manufacturers for non-medical reasons and the rapid development of successor clinical trials using novel targeted kinase inhibitors. Accrual to the study was open to members of ECOG-ACRIN, NCCTG, CALGB and SWOG. Patients were accrued by eight members (Mayo Clinic Rochester n=11, University of Wisconsin Hospital and Clinic n=8, Illinois CancerCare ORA COPP n=5, Dayton CCOP n=3, and one each by Penn State Medical Center, Gunderson Lutheran Health System CCOP, University of North Carolina at Chapel Hill, and University of Tennessee Health Science Center). This analysis reports on clinical data as of July 20, 2015. All enrolled patients were eligible, received treatment and were included in the analysis. Patient characteristics are summarized in Table I. The median age of 76 year (range 67–92) at age of study entry reflects the eligibility criteria with only three patients aged < 70 years enrolled after the age limit was lowered.

Twenty five patients (13 arm A and 12 arm B) completed treatment according to protocol with four receiving only two cycles of therapy because of achievement of CR with negative CT and negative bone marrow IHC minimal residual disease examination. Six patients (3 in each arm) did not complete therapy per protocol. Four stopped therapy because of toxicity, one patient in arm A decided to withdraw from the study and one patient in arm B stopped therapy at their physician's discretion because of deteriorating clinical condition without objective evidence of disease progression. Twenty two patients (eleven in each arm) had three cycles of therapy, seven (4 arms A and 3 arm B) had two cycles of therapy and two patients (one in each arm) had one cycle of therapy.

Treatment toxicity

Serious (> grade 2) adverse events at least possibly attributable to treatment are summarized in Table II. One patient (arm A) developed fatal progressive multifocal leukoencephalopathy (PML) and died 165 days after treatment initiation. Two additional patients had serious local infections and neutropenic fever occurred in the 3 of the 19 patients with grade 3–4 neutropenia. Of note, neutropenia occurred in more patients on standard dose rituximab (12 of 16, 75%) compared to patients on lower dose rituximab (7 of 15, 47%) but this difference was not statistically significant (p=0.15). Fifteen patients had CMV viremia with a median peak viral load of 2000 copies/ml (range of 398 – 55000) and were treated with valganciclovir with no treatment protocol interruptions and no hospitalizations.

Therapy Effect

Response—Twenty-eight patients (90%) responded to therapy with 14 (45%) CR, 3 (10%) CCR, and 11 (35%) PR. The ORR for higher frequency low dose rituximab treated patients (arm B) of 93.3% (14/15, 95% CI 68.1% – 99.8%) was not significantly different from the standard dose rituximab therapy (arm A) of 87.5% (14/16, 95% CI 61.7% – 98.5%) (p=1.0). The CR rate of 40% (6/15, 95% CI 16.3% – 67.7%) for arm B was not significantly different from the 50% (8/16, 95% CI 24.7% – 75.3%) for arm A (p =0.7).

Response duration—The median PFS for all patients was 17.9 months (95% confidence interval (CI) 12.4 – not achieved (NA)). The median PFS for arm B was longer than arm A but with overlapping confidence intervals (23.3 months, 95% CI 14.8 – NA vs. 12.8 months 95% CI 11.7 – NA) (Figure 1). Twenty-three patients were still alive with a median follow up time of 24.6 months (range 14.7 – 41.9 months). The median OS for the two arms have not been reached (Figure 2).

Discussion

We report a US Intergroup clinical trial testing a novel therapy for older patients with treatment naïve CLL. The regimen was designed to provide CLL patients with a tolerable response modulated alternative to chemo-immunotherapy. Treatment achieved high ORR and CR rates with tolerable toxicity but relatively short PFS. The treatment regimen became less accessible during the course of the trial because of withdrawal of alemtuzumab for CLL therapy and less likely to be used because of the remarkable and rapid development of targeted kinase inhibitor therapy for CLL. However, the study data remain informative for improving anti-CD20 mAb therapy in CLL.

The major toxicities of therapy with alemtuzumab and rituximab result from normal lymphocyte depletion. One patient in this study died from PML, which could be attributed to therapy-induced immunosuppression. PML has a reported incidence of 11 per 100,000 CLL patients per year. Although the most frequently reported association of PML in CLL patients has been with treatment regimens containing fludarabine and rituximab, PML has also been reported as a complication in treatment naïve CLL patients and those treated with alemtuzumab [20–22]. Previous studies of alemtuzumab containing regimens for the treatment of CLL reported high rates of Pneumocystis jiroveci, varicella zoster or herpes simplex related complications [23–25]. Antimicrobial prophylaxis was standard in this study and no patients had these complications. In previously reported studies of alemtuzumab as initial treatment of CLL the symptomatic CMV infection rate was 10 – 16% [23, 24]. Our use of a prospective weekly CMV monitoring approach showed a higher than expected rate of CMV reactivation in 15 patients (48%). This resulted from detecting subclinical reactivations and treatment of all 15 (48%) viremic patients avoided clinically evident CMV infection. We conclude that while opportunistic complications of CLL and its treatment such as PML are still unavoidable, a standardized pre-emptive approach to the common infectious complications can effectively manage the risk of infections with available prophylactic or preventative therapies. These data could be useful for managing patients with hematological

diseases such as T-cell prolymphocytic leukemia in which alemtuzumab remains an important therapeutic option.

Cytopenias were the most common serious adverse events in this study. The clinical significance of this finding is difficult to interpret because of use of the standard NCI Common Toxicity Criteria version 4, which does not account for pre-treatment cytopenias in CLL. Unfortunately the more appropriate grading scale for hematological toxicities in CLL studies currently used in many CLL studies [17] was not yet available during the planning of this study. The most common cytopenia was neutropenia (61%), which was complicated by neutropenic fever in three patients. Therapy with anti-CD20 mAb including rituximab and therapy with alemtuzumab can decrease neutrophil counts by mechanisms that are not fully understood [26, 27]. Of particular interest was the non-significant difference in the severe neutropenia rates in patients treated with low dose rituximab (7/15, 47%) compared to those on standard dose rituximab (12/16, 75%), which suggests that higher dose rituximab therapy could increase the risk of neutropenia.

There are no data from randomized controlled trials to determine if addition of rituximab to alemtuzumab therapy for CLL improves outcome. Previous clinical trials using alemtuzumab for initial treatment of progressive CLL resulted in high ORR as assessed by NCI-WG 1996 criteria. In a phase II trial enrolling 41 treatment naïve patients (median age 66 years) with progressive CLL for 18 weeks of therapy with subcutaneous alemtuzumab (planned therapy 18 weeks) the ORR was 87% with CR of 19% and the median time to treatment failure exceeded 18 months [23]. Similar results were achieved in the subset of 20 patients aged ≥65 years (ORR 90%, CR 20%) [23]. In a randomized phase III trial comparing IV alemtuzumab to chlorambucil for initial therapy of progressive CLL, the 149 patients in the alemtuzumab cohort (median age 59 years) had an ORR of 83% with 24% CR and median PFS of 11.7 months [24]. The subset of 53 patients on the alemtuzumab arm aged ≥65 years had a similar reported outcome (ORR 76% and median PFS 12.5 months). In our study the CR rate using more rigorous IWCLL 2008 compatible response criteria including CT scans was 45%. This suggests that addition of rituximab to alemtuzumab could improve the depth of response to treatment and possible also the PFS.

There has been a considerable progress in improving CLL therapies for less fit patients. Addition of anti-CD20 mAbs to oral chlorambucil has been shown to improve the quality and duration of responses. A clinical trial enrolling a total of 781 patients (median age 73 years) requiring initial treatment for progressive CLL randomized patients to chlorambucil alone or in combination with either rituximab or obinutuzumab with responses assessed with IWCLL 2008 criteria [28]. Compared to an ORR rate of 31% (no CR, median PFS 11 months) with chlorambucil monotherapy, addition of rituximab significantly increased the ORR rate to 66% (7% CR, median PFS 16 months) and addition of obinotuzumab significantly increased the ORR to 77% (22% CR, median PFS 27 months). Another large clinical trial enrolled 447 patients (median age 69 years) requiring initial therapy for progressive CLL who were randomized to chlorambucil monotherapy or chlorambucil and ofatumumab [29]. The responses were significantly higher in the patients treated with chlorambucil and ofatumumab (ORR 82% vs 69%, CR 14% vs. 1%, median PFS 22 vs. 13 months). A recently reported phase II study of combination initial therapy for 70 elderly

patients (median age 72 years) with CLL using bendamustine and rituximab achieved a ORR of 89% with 31% CR and median PFS of 79% at 2 years [30]. The mAb combination therapy used in our trial achieved an ORR and CR comparable to these chemoimmunotherapy regimens but with a shorter PFS. The reason for this discrepancy is currently unknown and further investigation could be informative about the differences in the cytotoxic effects of mAb compared to DNA damaging agents.

To the best of our knowledge this is the first study to randomize patients to either a higher frequency low dose or standard dose anti-CD20 mAb therapy. Use of the lower dose regimen did not appear to affect ORR or CR rates with no significant difference in PFS but these data have to be considered preliminary because of the small sample size. An additional potential advantage of the low dose rituximab regimen could be a decreased risk of iatrogenic neutropenia. The need to administer rituximab IV three times a week did increase the logistical burden on patients randomized to arm B of the study, but the development of subcutaneous formulations for rituximab and ofatumumab could allow patients to be trained to self-administer low doses of these mAb at home as was done for alemtuzumab for many patients on this study. These data add to the preclinical data [31–34] and clinical study data [12–14] that suggest that subcutaneous low dose higher frequency anti-CD20 mAb therapy could be a better therapy for CLL than currently used regimens. The addition of low dose higher frequency anti-CD20 mAb therapy to B-cell receptor pathway inhibitors could potentially improve the efficacy and safety of therapy for CLL.

The strengths of this study include treatment at eight sites including a mix of academic and community based centers, inclusion of an older population with predominantly advanced stage disease and a high proportion of genetically high risk disease, and the use of imaging and bone marrow immunohistochemistry to determine responses to treatment. The study also shows that a shorter duration combination antibody therapy can be effectively administered with tolerable toxicity and achieve a high response rate. The major limitation of this study is the limited accrual due to immutable circumstances. The paradigm shift in management of CLL that occurred during the conduct of this clinical trial markedly decreased the clinical value of our data on use of alemtuzumab for treatment of older patients with CLL. Despite these limitations, this study does provide preliminary data that could be useful in improving use of anti-CD20 mAb therapy, which continues to be very valuable in the treatment of CLL and other B cell malignancies.

In conclusion, we present data showing that a mAb combination therapy was effective and tolerable therapy for the initial treatment of progressive CLL in older patients. Although this regimen has been superseded by progress in targeted drug development, the data on the use of anti-CD20 mAb is informative for designing future clinical trials and correlative studies to optimize use of this class of drugs that continues to have an important role in the management of this incurable disease.

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References

1. Howlader, N.; Noone, A.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2012. National Cancer Institute; Bethesda, MD: 2015. http://seer.cancer.gov/csr/1975_2012/
2. Keating MJ, O'brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005; 23:4079–4088. [PubMed: 15767648]
3. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010; 376:1164–1174. [PubMed: 20888994]
4. Taylor RP, Lindorfer MA. Analyses of CD20 Monoclonal Antibody-Mediated Tumor Cell Killing Mechanisms: Rational Design of Dosing Strategies. Molecular pharmacology. 2014; 86:485–491. [PubMed: 24944188]
5. Golay J, Introna M. Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays. Archives of biochemistry and biophysics. 2012; 526:146–153. [PubMed: 22387378]
6. Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood. 2003; 101:3413–3415. [PubMed: 12522009]
7. Nabhan C, Patton D, Gordon L, et al. A Pilot Trial of Rituximab and Alemtuzumab Combination Therapy in Patients with Relapsed and/or Refractory Chronic Lymphocytic Leukemia (CLL). Leuk Lymphoma. 2004; 45:2269–2273. [PubMed: 15512816]
8. Zent CS, Call TG, Shanafelt TD, et al. Early treatment of high risk chronic lymphocytic leukemia with alemtuzumab and rituximab. Cancer. 2008; 113:2110– 2118. [PubMed: 18759253]
9. Zent CS, Wu W, Bowen DA, et al. Addition of GM-CSF does not improve response to early treatment of high risk chronic lymphocytic leukemia with alemtuzumab and rituximab. Leuk Lymphoma. 2013; 54:476–482. [PubMed: 22853816]
10. Frankfurt O, Ma S, Gordon L, et al. Phase II study of alemtuzumab-rituximab therapy in previously untreated patients with chronic lymphocytic leukemia: short-and long-term outcomes. Leuk Lymphoma. 2014:1–9.
11. Zent CS, Call TG, Bowen DA, et al. Early treatment of high risk chronic lymphocytic leukemia with alemtuzumab, rituximab and poly-(1–6)-beta-glucotriosyl-(1–3)-beta-glucopyranose beta-glucan is well tolerated and achieves high complete remission rates. Leuk Lymphoma. 2015; 56:2373–2378. [PubMed: 25676035]
12. Williams ME, Densmore JJ, Pawluczkowycz AW, et al. Thrice-weekly low-dose rituximab decreases CD20 loss via shaving and promotes enhanced targeting in chronic lymphocytic leukemia. J Immunol. 2006; 177:7435–7443. [PubMed: 17082663]
13. Aue G, Lindorfer MA, Beum PV, et al. Fractionated subcutaneous rituximab is well-tolerated and preserves CD20 expression on tumor cells in patients with chronic lymphocytic leukemia. Haematologica. 2010; 95:329–332. [PubMed: 19679883]
14. Zent CS, Taylor RP, Lindorfer MA, et al. Chemoimmunotherapy for relapsed/refractory and progressive 17p13 deleted chronic lymphocytic leukemia (CLL) combining pentostatin, alemtuzumab, and low dose rituximab is effective and tolerable and limits loss of CD20 expression by circulating CLL cells. American journal of hematology. 2014; 89:757–765. [PubMed: 24723493]
15. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. Blood. 1996; 87:4990–4997. [PubMed: 8652811]
16. Muller-Hermelink, HK.; Catovsky, D.; Montserrat, E., et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma. In: Jaffe, E.; Harris, N.; Stein, H., et al., editors. Tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001. p. 127-130.

17. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood. 2008; 111:5446–5456. [PubMed: 18216293]
18. Zelen M. The randomization and stratification of patients to clinical trials. J Chronic Dis. 1974; 27:365–375. [PubMed: 4612056]
19. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–481.
20. Herold T, Seiler T, Egensperger R, et al. Progressive multifocal leukoencephalopathy after treatment with rituximab, fludarabine and cyclophosphamide in a patient with chronic lymphocytic leukemia. Leuk Lymphoma. 2012; 53:169–172. [PubMed: 21812535]
21. Di Pauli F, Berger T, Walder A, et al. Progressive multifocal leukoencephalopathy complicating untreated chronic lymphatic leukemia: case report and review of the literature. J Clin Virol. 2014; 60:424–427. [PubMed: 24929753]
22. Isidoro L, Pires P, Rito L, et al. Progressive multifocal leukoencephalopathy in a patient with chronic lymphocytic leukaemia treated with alemtuzumab. BMJ Case Rep. 2014; 2014
23. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood. 2002; 100:768–773. [PubMed: 12130484]
24. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007; 25:5553–5555. [PubMed: 17984184]
25. Elter T, Vehreschild JJ, Gribben J, et al. Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. Annals of hematology. 2009; 88:121–132. [PubMed: 18682948]
26. Ambrose LR, Morel AS, Warrens AN. Neutrophils express CD52 and exhibit complement-mediated lysis in the presence of alemtuzumab. Blood. 2009; 114:3052–3055. [PubMed: 19638623]
27. Dunleavy K, Tay K, Wilson WH. Rituximab-associated neutropenia. Seminars in hematology. 2010; 47:180–186. [PubMed: 20350665]
28. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. The New England journal of medicine. 2014; 370:1101–1110. [PubMed: 24401022]
29. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015; 385:1873–1883. [PubMed: 25882396]
30. Laurenti L, Innocenti I, Autore F, et al. Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: A retrospective analysis of real-life practice in Italian hematology departments. Leukemia research. 2015; 39:1066–1070. [PubMed: 26307523]
31. Kennedy AD, Beum PV, Solga MD, et al. Rituximab infusion promotes rapid complement depletion and acute CD20 loss in chronic lymphocytic leukemia. J Immunol. 2004; 172:3280–3288. [PubMed: 14978136]
32. Beum PV, Kennedy AD, Williams ME, et al. The shaving reaction: rituximab/CD20 complexes are removed from mantle cell lymphoma and chronic lymphocytic leukemia cells by THP-1 monocytes. J Immunol. 2006; 176:2600– 2609. [PubMed: 16456022]
33. Beurskens FJ, Lindorfer MA, Farooqui M, et al. Exhaustion of cytotoxic effector systems may limit monoclonal antibody-based immunotherapy in cancer patients. J Immunol. 2012; 188:3532–3541. [PubMed: 22368276]
34. Baig NA, Taylor RP, Lindorfer MA, et al. Induced resistance to ofatumumab-mediated cell clearance mechanisms, including complement-dependent cytotoxicity, in chronic lymphocytic leukemia. J Immunol. 2014; 192:1620–1629. [PubMed: 24431228]

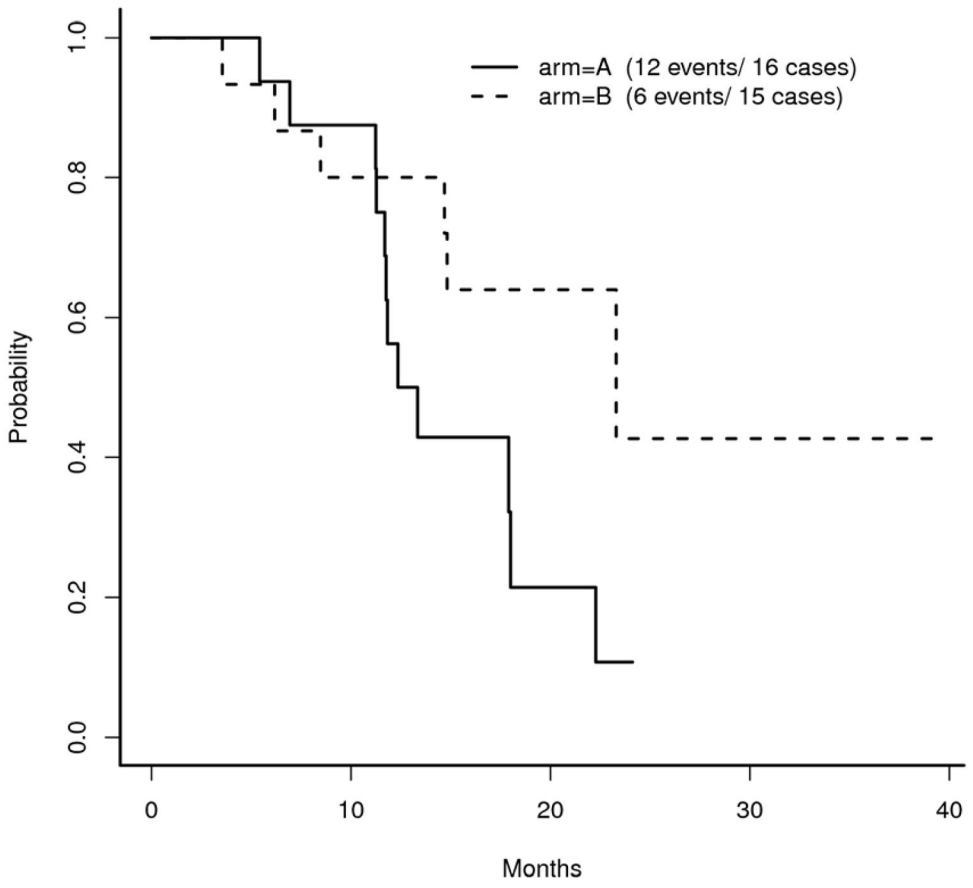

Figure 1. Progression free survival

The median progression free survival for patients treated with standard dose rituximab (arm A) was 12.8 months with a 95% confidence interval (CI) of 11.7 – not achieved (NA) and for patients treated with higher frequency low dose rituximab (arm B) was 23.3 months with 95% CI of 14.8 – NA.

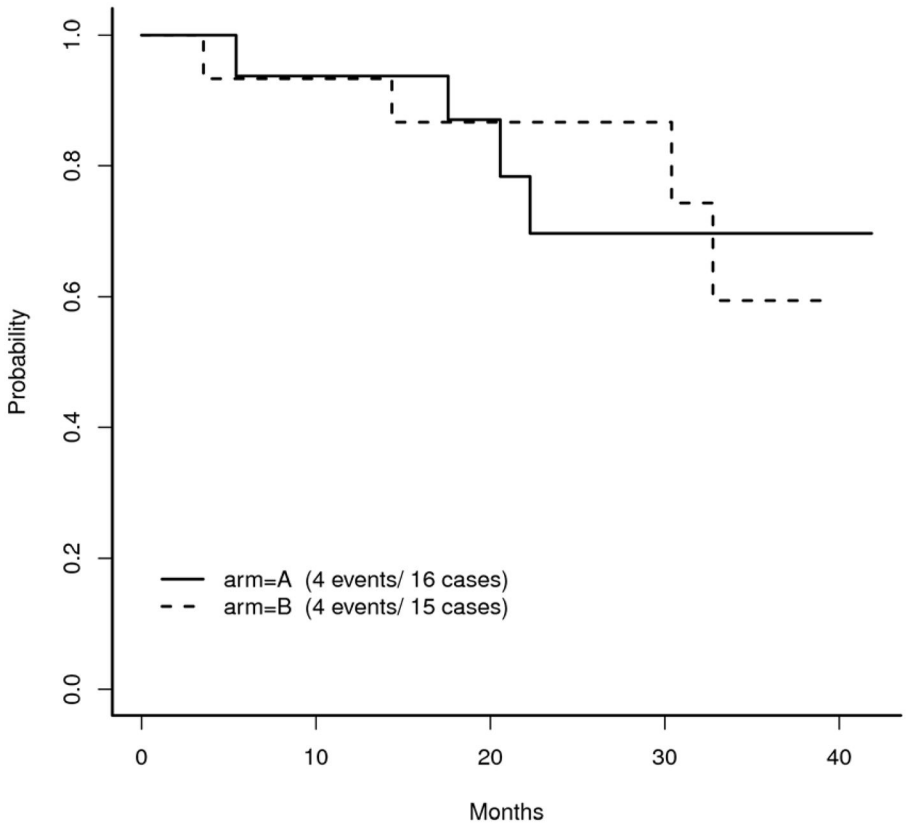

Figure 2. Overall Survival

Median overall survival has not been reached for either treatment arm with 23 surviving patients having a median follow up time of 24.6 months (range 14.7 – 41.9 months).

Table I

Patient Characteristics

		A n=16	B n=15	All n=31
Age (years)	Median	77	76	76
	Range	67–92	68–86	67–92
Gender[*]	Male	10 (62.5)	8 (53.3)	18 (58.1)
	Female	6 (37.5)	7 (46.7)	13 (41.9)
Performance status (ECOG)	0	10 (62)	4 (27)	14 (45)
	1	5 (31)	10 (67)	15 (48)
	2	1 (6)	1 (7)	2 (6)
Clinical Stage (Rai)	0	0 (0)	1 (7)	1 (3)
	I	3 (19)	1 (7)	4 (13)
	II	1 (6)	1 (7)	2 (6)
	III	7 (44)	9 (60)	16 (52)
	IV	5 (31)	3 (20)	8 (26)
Risk Stratification (FISH)	High[#]	5 (31)	4(27)	9 (29)
	Intermediate	6 (38)	6 (40)	12 (39)
	Low	5 (31)	5 (33)	10 (32)

[*] number of patients and (%)

[#] Five patients with 17p13 deletion (3 on arm A and 2 on arm B) and 4 patients with 11q22 deletion (2 on each arm)

Table II

Severe Adverse Events

Adverse Event*	A n=16	B n=15	Total
Anemia	1	1	2
Febrile neutropenia	2	1	3
Neutropenia	12	7	19
Thrombocytopenia	3	1	4
Fatigue	2	1	3
Rash		2	2
Mucositis	1		1
Serum sickness		1	1
Infection - lung		1	1
Infection - tooth	1		1
Infection - CNS	1#		1
Lipase increased	1		1
Weight loss	1		1
Hyponatremia	1	1	2

*greater than grade 2 toxicity at least possibly attributable to treatment

#patient died of progressive multifocal leukoencephalopathy