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ORIGINAL REPORT

Alemtuzumab Compared With Chlorambucil As First-Line Therapy for Chronic Lymphocytic Leukemia

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ABSTRACT

Purpose
We conducted a randomized trial to evaluate the efficacy and safety of intravenous alemtuzumab compared with chlorambucil in first-line treatment of chronic lymphocytic leukemia (CLL).

Patients and Methods
Patients received alemtuzumab (30 mg three times per week, for up to 12 weeks) or chlorambucil (40 mg/m^2 every 28 days, for up to 12 months). The primary end point was progression-free survival (PFS). Secondary end points included overall response rate (ORR), complete response (CR), time to alternative therapy, safety, and overall survival.

Results
We randomly assigned 297 patients, 149 to alemtuzumab and 148 to chlorambucil. Alemtuzumab had superior PFS, with a 42% reduction in risk of progression or death (hazard ratio [HR] = 0.58; P = .0001), and a median time to alternative treatment of 23.3 versus 14.7 months for chlorambucil (HR = 0.54; P = .0001). The ORR was 83% with alemtuzumab (24% CR) versus 55% with chlorambucil (2% CR); differences in ORR and CR were highly statistically significant ($P < .0001$). Elimination of minimal residual disease occurred in 11 of 36 complete responders to alemtuzumab versus none to chlorambucil. Adverse events profiles were similar, except for more infusion-related and cytomegalovirus (CMV) events with alemtuzumab and more nausea and vomiting with chlorambucil. CMV events had no apparent impact on efficacy.

Conclusion
As first-line treatment for patients with CLL, alemtuzumab demonstrated significantly improved PFS, time to alternative treatment, ORR and CR, and minimal residual disease–negative remissions compared with chlorambucil, with predictable and manageable toxicity.

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INTRODUCTION

Molecular heterogeneity in chronic lymphocytic leukemia (CLL) is associated with prolonged survival in some patients, whereas others have a very poor prognosis.[1] Options for first-line therapy include chlorambucil,[2,3] the only agent with a US Food and Drug Administration–approved indication for first-line use in CLL (until the recent approval of alemtuzumab), and the purine analog fludarabine.[4,5] Combination chemotherapy for CLL has resulted in improved response rates and progression-free survival (PFS), but not yet overall survival.[6,7] The eradication of detectable minimal residual disease (MRD) has been associated with improved survival.[8] New strategies for treatment of CLL will incorporate the most active agents and be tailored for patient-specific molecular disease characteristics.

According to the Döhner hierarchical model,[1] the worst disease progression and survival outcomes correlate with deletions of 17p (the location of the p53 gene) and 11q. Mutations in p53 are associated with resistance to chemotherapy, particularly to purine analogs, and shortened survival in CLL,[9-12] most likely because these agents induce apoptosis through p53-dependent pathways.[13] It is important to identify treatments for CLL that work through p53-independent mechanisms and eradicate MRD.

Alemtuzumab is a recombinant, humanized, monoclonal antibody directed against CD52, a cell surface protein highly expressed on most normal and malignant B and T lymphocytes,[14] but not on hematopoietic stem cells.[15] In patients with relapsed or refractory CLL after fludarabine and alkylator therapy alemtuzumab induced a 33% overall response rate (ORR), including some complete responses (CRs), with additional clinical benefit seen

in patients with stable disease.[16] The most common toxicities were grade 1 to 2 acute infusion reactions, cytopenias, and a cytopenia-related vulnerability to infections. Alemtuzumab has efficacy in patients with fludarabine-refractory CLL and chromosome 17p deletions or *p53* gene mutations.[17-19] Alemtuzumab eradicates MRD in some patients with CLL, which has been associated with improved survival.[8,20,21] A phase II study of subcutaneously administered alemtuzumab in first-line CLL showed an improved safety profile and ORR of 87%, including 19% CR.[22,23]

CAM307 was an international, multicenter, randomized, open-label phase III trial comparing alemtuzumab with chlorambucil in previously untreated patients requiring treatment for CLL. The primary end point of CAM307 was PFS. Secondary end points included response rates, time to alternative treatment, overall survival, and safety.

PATIENTS AND METHODS

Patients

Eligible patients were at least 18 years old with flow cytometry–confirmed diagnosis of B-cell CLL, Rai stage I through IV with evidence of progression according to National Cancer Institute Working Group (NCI-WG) 1996 criteria,[24] no previous chemotherapy for CLL, a life expectancy of at least 12 weeks, WHO performance status of 0 to 2, and adequate renal and liver function. Exclusion criteria included chronic oral corticosteroid use, autoimmune thrombocytopenia, previous bone marrow transplant, CLL with CNS involvement, positive quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) assay, positivity for HIV, and presence of active infection. Pretreatment cytogenetic analysis was performed by fluorescent in situ hybridization on peripheral blood. Results of cytogenetic analyses were not used as criteria for study entry or stratification. All patients provided written informed consent.

Treatment Plan

Patients were randomly assigned to alemtuzumab or chlorambucil (Fig A1, online only). Treatment arm assignment was balanced by study center, Rai stage (I to II *v* III/IV), performance status (0 to 1 *v* 2), age (< 65 *v* ≥ 65 years), sex, and maximum lymph node size (none palpable or < 5 *v* ≥ 5 cm).

Alemtuzumab was escalated daily (3, 10, and 30 mg) until tolerated at an intravenous (IV) dose of 30 mg over 2 hours. Subsequently, patients received alemtuzumab 30 mg three times a week for no more than 12 weeks, including the dose-escalation phase. Premedication for alemtuzumab consisted of diphenhydramine and acetaminophen or paracetamol orally (PO) 30 minutes before dosing, with optional IV meperidine or hydrocortisone when warranted. During the first month of treatment, patients received allopurinol days -1 to 13. Patients received prophylactic trimethoprim/sulfamethoxazole DS and famciclovir (or equivalents) during therapy and for at least 2 months after the last alemtuzumab dose or until $CD4^+$ counts were 200 cells/μL or higher.

Alemtuzumab was interrupted during serious infection or grade 3 or worse pulmonary, renal, or hepatic toxicity. A positive PCR assay for CMV was to have led to therapy interruption, with a repeat CMV PCR assay performed 1 week later. Therapy was resumed in asymptomatic patients with negative repeat assays. A positive follow-up PCR assay or signs/symptoms consistent with active CMV disease led to treatment interruption and IV ganciclovir or equivalent therapy. Treatment was discontinued if delayed for more than 4 weeks.

Patients in the chlorambucil arm received 40 mg/m^2 PO q 28 days for no more than 12 cycles with allopurinol PO days -1 to 8 for the first three cycles. Prophylactic antibiotics were not required. Treatment was interrupted for grade 3 or higher toxicities, with chlorambucil reduced by 50% if dose was restarted after interruption for grade 3 or worse pulmonary, renal, hepatic, or other nonhematologic toxicity.

Treatment was to be discontinued in both arms if a patient experienced progressive disease, unacceptable toxicity, autoimmune anemia, or autoimmune thrombocytopenia. Subsequent treatment was at the discretion of the treating physician.

Evaluation During Study

Patients were evaluated by physical examination, laboratory data, and chest x-ray (during treatment only) as indicated, and then monthly until disease progression, administration of alternative therapy, or through 18 months after first dose. Afterward, patients were followed up every 3 months for disease progression or survival.

An independent response review panel, blinded to treatment assignment, confirmed CLL diagnosis and Rai stage and determined response and date of disease progression for each patient. Adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0.

In the alemtuzumab arm, CMV testing by PCR occurred weekly during therapy and every 2 weeks for 2 months after completion of therapy. In the chlorambucil arm, PCR CMV testing occurred monthly during therapy, at end of therapy, and 1 month after stopping therapy. Direct and indirect Coombs tests were performed at baseline, monthly during study treatment, and at end of treatment for both arms.

Flow Cytometry and Cytogenetic Analyses

Flow cytometry was performed on peripheral blood before and on study to monitor response and, when available, on bone marrow aspirates before therapy and when repeated to assess response. At study entry, interphase fluorescent in situ hybridization analysis used 13 DNA probes to detect chromosomal aberrations in 17p13.1 (*p53*), 13q14 (*RB1*, D13S319 and D13S25), 11q22-11q23 (*ATM* and *MLL*), 6q27 (subtelomere), 6q21 (chromosome 6q21/alphasatellite 6 cocktail probe), trisomy 8q24 (c-*myc*), trisomy 12q13 (CEP12) and translocations involving the locus of immunoglobulin heavy chain gene (*IGH*, 14q32.33). Cytogenetic and MRD analyses were performed by central laboratories.

Response Criteria and Assessment of Complete Responders

Response criteria and progression were defined according to the NCI-sponsored Working Group response criteria for CLL.[24] Patients with a clinical CR were to have a confirmatory bone marrow aspirate and biopsy 8 weeks after the end of treatment. Assessment for MRD was performed by four-color flow cytometry ($CD5^+/CD19^+/CD52^+/\kappa^+$ or λ^+) of peripheral blood and bone marrow.

Statistical Analysis

The planned sample size was 284 patients (142 per arm) to allow detection of a 50% increase in median PFS in either arm (hazard ratio [HR] = 0.667), with 80% power and $\alpha = .05$ (two-sided). A preplanned interim analysis was performed after 95 progressions, and the final analysis was performed at a significance level of .048 using the O'Brien-Fleming methodology to ensure the overall significance level of .05. All randomly assigned patients were included in the efficacy analysis per the intent-to-treat principle. Safety was analyzed for all patients who received at least one dose of study drug. All time-to-event distributions were calculated using Kaplan-Meier method, reported in months, and compared using stratified (Rai stage I to II *v* III to IV) log-rank test. HRs were calculated using Cox model stratified for Rai stage. Response rates were compared using χ^2 test or Fisher's exact test, as appropriate. PFS was defined from the date of random assignment to first objective documentation of disease progression or death, whichever was earlier. Time to alternative treatment was defined from date of random assignment to the date of first alternative treatment or death resulting from any cause.

A total of 191 disease progression or death events (82 in the alemtuzumab arm and 109 in the chlorambucil arm) were used for the final analysis of PFS. All the efficacy analyses were based on the independent response review panel's assessment of eligibility, response, and date of progression.

RESULTS

Patients

From December 2001 to July 2004, 297 patients were enrolled and randomly assigned to alemtuzumab (n = 149) or chlorambucil

(n = 148) treatment at 44 centers (nine in the United States, 35 in Europe). Three patients (two assigned to alemtuzumab and one to chlorambucil) withdrew consent before treatment administration and were not included in the safety analysis. Baseline demographic and disease characteristics were well balanced between the groups (Table 1). Results from 282 patients were used for cytogenetic subgroup analyses.

Treatment Duration

The same number of patients (n = 147) in both arms received at least 1 administration of study drug. The median length of alemtuzumab exposure was 11.7 weeks (range, 0 to 33 weeks), inclusive of treatment delays, and the median cumulative dose was 956 mg (range, 2 to 1,645 mg). Nearly all patients, 143 (97.3%) of 147, received the alemtuzumab 30 mg target dose, with 85.7% reaching this target within 5 calendar days. Most patients (71.4%) were treated with 21 or more doses of alemtuzumab 30 mg.

The median length of chlorambucil exposure was 28.3 weeks (range, 4 to 59 weeks), with a 515-mg median cumulative dose (range, 60 to 1,168 mg) and median 7 cycles (range, one to 12 cycles).

Efficacy

PFS. Alemtuzumab was superior to chlorambucil as measured by PFS (stratified log-rank $P = .0001$). After adjustment by Rai stage group (I to II *v* III/IV), the HR for PFS was 0.58 (95% CI, 0.43 to 0.77), for a 42% reduction in the risk of disease progression or death (Fig 1A). Better response appeared to correlate with longer PFS in alemtuzumab-treated patients (Fig 1B).

Response Rates

The ORR and CR rate were significantly higher ($P < .0001$) for alemtuzumab (Table 2). In the intent-to-treat population, MRD was undetectable in 11 of 36 CRs to alemtuzumab.

Time to Alternative Treatment

Patients receiving alemtuzumab experienced a significantly longer median time to alternative treatment compared with those receiving chlorambucil (stratified log-rank $P = .0001$), despite a shorter duration of therapy. The median time to alternative therapy was 23.3 months (95% CI, 20.7 to 31.0 months) for alemtuzumab, with a median 11.7 weeks of therapy, and 14.7 months (95% CI, 12.6

Table 1. Baseline Patient Characteristics and Cytogenetics

Characteristic	Alemtuzumab (n = 149)		Chlorambucil (n = 148)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	59.0		60.0	
Range	35–86		36–83	
Sex				
Male	106	71.1	107	72.3
Female	43	28.9	41	27.7
Rai stage group (IRRP)				
0 or missing*	6	4.0	3	2.0
I-II	93	62.4	96	64.9
III/IV	50	33.6	49	33.1
Time since initial diagnosis to random assignment, months				
Median	9.38		7.85	
Range	−0.5-167.4†		0.1-224.8	
Maximum lymph node size, cm				
< 5	107	71.8	104	70.3
≥ 5	33	22.1	34	23.0
No enlarged lymph nodes	8	5.4	10	6.8
Palpable hepatomegaly	43	28.9	27	18.2
Palpable splenomegaly	53	35.6	56	37.8
WHO performance status				
0-1	143		143	
2	5	3.4	5	3.4
Night sweats	64	43.0	69	46.6
Weight loss > 10%	9	6.0	16	10.8
Fever	1	0.7	2	1.4
Hierarchical cytogenetic subgroups‡				
17p13.1 (p53)	11	7.7	10	7.2
Any del 11q	23	16.1	31	22.3
Trisomy 12 (no 11p or 17p del)	24	16.8	10	7.2
Normal	25	17.5	26	18.7
Sole del 13q	33	23.1	34	24.5
Various other combinations	27	18.9	28	20.1

Abbreviations: IRRP, independent response review panel; CLL, chronic lymphocytic leukemia; del, deletion.
*These patients were assessed as Rai stage 0 (n = 5) and unconfirmed for B-cell CLL diagnosis (n = 4) by the IRRP.
†One patient was inadvertently randomly assigned prior to completion of CLL diagnosis.
‡According to the hierarchical Döhner et al[1] method, n = 143 for the alemtuzumab group and n = 139 for the chlorambucil group.

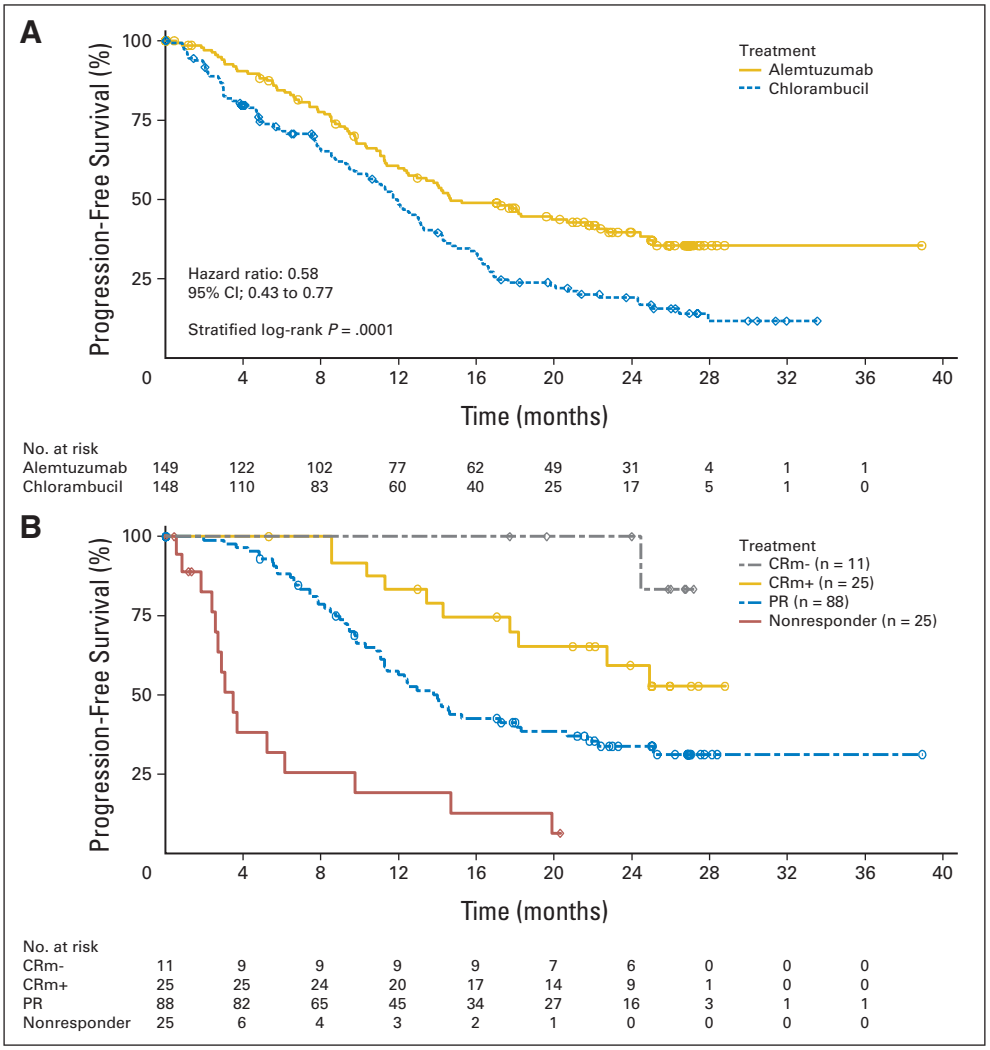

Fig 1. (A) Kaplan-Meier estimates of progression-free survival (PFS) based on Independent Response Review Panel. Overall median PFS was 14.6 months (95% CI, 12.3 to 21.7 months) for patients in the alemtuzumab arm and 11.7 months (95% CI, 9.9 to 13.2 months) for patients in the chlorambucil arm (stratified log-rank $P = .0001$). Median follow-up was 24.5 months for alemtuzumab and 24.9 months for chlorambucil. (B) Kaplan-Meier estimates of PFS according to response in the alemtuzumab arm. With a median follow-up of 2 years, only one CRm– patient has progressed. CR, complete response; MRD, minimal residual disease; CRm–, MRD negative CR; CRm+, MRD positive CR; PR, partial response.

to 16.8 months) for chlorambucil, with a median 28.3 weeks of therapy. Thus, alemtuzumab treatment resulted in a treatment-free period of approximately 88 weeks compared with 36 weeks for chlorambucil.

Table 2. Treatment Response by IRRP

Response Category	Alemtuzumab (n = 149) No. of Patients	Alemtuzumab (n = 149) %	Chlorambucil (n = 148) No. of Patients	Chlorambucil (n = 148) %	*P*
Overall responses	124	83.2	82	55.4	< .0001
CR	36	24.2	3	2.0	< .0001
MRD-negative*	11	7.4	0	0	.0008
Partial response	88	59.1	79	53.4	—
Stable disease	9	6.0	42	28.4	—
Progressive disease	5	3.4	18	12.2	—
Not assessable	11	7.4	6	4.1	—

Abbreviations: IRRP, independent response review panel; CR, complete response; MRD, minimal residual disease.
*Two MRD-CR patients were determined by the IRRP to be Rai stage 0 at study entry.

Outcome by Cytogenetic Group and Stratification Factor

Chromosomal aberrations were categorized according to Döhner's hierarchical model.[1] Table 3 provides the efficacy results by genetic aberrations, and Table 4 shows the efficacy results by stratification factor.

Overall Survival

Median overall survival has not yet been reached for either arm. After a median follow-up of 24.6 months, 84% of patients in each arm were alive at the data cutoff or at the last follow-up dates. Further information on overall survival is not expected.

Safety

AEs. AEs during the treatment period and within 30 days of last study dose are shown in Table 5. Infusion-related events in the alemtuzumab arm included fever, chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, vomiting, and bronchospasm, and decreased after the first week of therapy.

Sixteen patients (11%) treated with alemtuzumab and 26 patients (18%) treated with chlorambucil had grade 3 to 4 anemia, with a median time to onset of 4.4 and 8.1 weeks, respectively. Sixty patients

Table 3. ORR and PFS by Treatment Arm According to Cytogenetic Abnormality

Deletion	Alemtuzumab				Chlorambucil				*P*	
		ORR				ORR				
	No. of Patients	No. of Patients	%	Median PFS (months)	No. of Patients	No. of Patients	%	Median PFS (months)	ORR	PFS
17p del	11	7	64	10.7	10	2	20	2.2	.0805	.4066
11q del (no 17p del)	23	20	87	8.5	31	9	29	8.5	< .0001	.4338
Trisomy 12 (no 17p del, no 11q del)	24	20	83	18.3	10	8	80	12.9	1.0000	.0915
Normal	25	21	84	19.9	26	18	69	14.3	.3238	.5582
Sole 13q	33	30	91	24.4	34	21	62	13.0	.0087	.0170
17p del or 11q del	34	27	79	9.4	41	11	27	7.7	< .0001	.1602

NOTE. Data presented according to the hierarchical model of Döhner et al,[1] plus an additional analysis combining 17p del and 11q del.
Abbreviations: ORR, overall response rate; PFS, progression-free survival; del, deletion.

(41%) receiving alemtuzumab and 36 patients (25%) receiving chlorambucil had grade 3 to 4 neutropenia ($P = .0041$), with a median time to onset of 4.4 and 3.7 weeks, respectively. Eighteen patients (12%) receiving alemtuzumab and 17 patients (12%) receiving chlorambucil had grade 3 to 4 thrombocytopenia, with a median time to onset of 1.3 and 7.9 weeks, respectively.

In the alemtuzumab arm, four (33%) of 12 patients with a baseline positive direct Coombs test converted to a negative test during treatment, and four (3%) of 132 patients with a negative baseline direct Coombs test had a positive test during treatment. In the chlorambucil arm, one (7%) of 15 patients with a baseline positive direct Coombs test had a negative direct Coombs test during treatment, and eight (6%) of 125 patients with a negative baseline direct Coombs test had a positive test during treatment. In the alemtuzumab arm, one patient developed hemolytic anemia (related to malignancy) 4 months after last dose of study drug. In the chlorambucil arm, two patients developed hemolytic anemia (one related to study drug and one related to malignancy) while receiving study drug.

Although grade 3 to 4 neutropenia was more common in the alemtuzumab arm, febrile neutropenia (4.8% with alemtuzumab and 2.7% with chlorambucil) and bacteremia/sepsis (3% and 1.4%, respectively) were similarly uncommon. Growth factor support was administered to 9.5% of patients receiving alemtuzumab and 4.1% receiving chlorambucil.

Serious AEs and Discontinuation Resulting From AEs

Serious drug-related AEs were more common in the alemtuzumab arm (26.5% *v* 6.8%), but in some institutions, asymptomatic PCR-positive CMV was reported as a serious AE because routine medical practice or social circumstances required hospital admission for treatment with IV ganciclovir. When considering drug-related serious AEs, the only events more common for patients receiving alemtuzumab were CMV events. Drug-related AEs that led to permanent discontinuation of study drug were reported for 19.7% of patients receiving alemtuzumab and 4.1% of patients receiving chlorambucil. In the alemtuzumab arm, 17 patients discontinued from the study because of drug-related grade 3/4 toxicity: six grade 3 CMV events, n = 1 tuberculosis, n = 1 bronchopneumonia, n = 2 neutropenia, n = 1 thrombocytopenia, and n = 1 each urticaria, hypotension with sinus bradycardia, cardiac arrest (with immediate recovery), dyspnea and hypersensitivity, bronchospasm, and atrial fibrillation. In the chlorambucil arm, five patients discontinued from the study because of grade 3 to 4 drug-related AEs: n = 2 grade 3

Table 4. ORR and PFS By Treatment Arm According to Stratification Factor

Factor	Alemtuzumab				Chlorambucil				*P*	
		ORR				ORR				
	No. of Patients	No. of Patients	%	Median PFS (months)	No. of Patients	No. of Patients	%	Median PFS (months)	ORR	PFS
Age, years										
≥ 65	53	40	76	12.5	52	29	56	12.5	.0409	.2131
< 65	96	84	88	17.7	96	53	55	11.7	< .0001	< .0001
Sex										
Male	106	94	89	14.1	107	54	51	12.0	< .0001	.0020
Female	43	30	70	24.9	41	28	68	11.7	1.0000	.0221
Maximum node size, cm										
≥ 5	33	25	76	11.1	34	15	44	8.8	.0125	.2195
< 5	115	99	86	17.7	114	67	59	12.5	< .0001	.0003
Performance status										
0-1	143	121	85	14.7	143	82	57	12.0	< .0001	.0002
2	5	3	60	7.4	5	0	0	3.5	.1667	.4245

Abbreviations: ORR, overall response rate; PFS, progression-free survival.

Table 5. Toxicities Reported for ≥ 10% of Patients

Adverse Event	Alemtuzumab (n = 147)				Chlorambucil (n = 147)			
	All Grades		Grade 3/4		All Grades		Grade 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Infusion related								
Pyrexia	94	63.9	12	8.2	5	3.4	—	—
Chills	73	49.7	5	3.4	—		—	—
Urticaria	22	15.0	3	2.0	1	0.7	—	—
Hypotension	21	14.3	2	1.4	—		—	—
Rash	18	12.2	1	0.7	1	0.7	—	—
CMV events*								
Asymptomatic CMV with PCR positivity	77	52.4	6	4.1	11	7.5	—	—
Symptomatic CMV infection	23	15.6	6	4.1	—		—	—
Nausea	19	12.9	—	—	51	34.7	1	0.7
Vomiting	10	6.8	—	—	27	18.4	1	0.7

NOTE. Toxicities are treatment related, except for CMV events, which are reported regardless of relatedness. Grade refers to National Cancer Institute Common Toxicity Criteria Version 2.0.
Abbreviations: CMV, cytomegalovirus; PCR, polymerase chain reaction.

thrombocytopenia, n = 1 grade 3 leukopenia, n = 1 *Listeria monocytogenes* encephalitis, and n = 1 pneumonia.

Four patients died during treatment or within 30-days of last study drug dose, one (0.6%) in the alemtuzumab arm of *Candida albicans* deemed unrelated to treatment and three (2.0%) in the chlorambucil arm, one of *Listeria monocytogenes* encephalitis attributed to treatment, one of sudden death attributed to other causes, and one of cardiac insufficiency. There were no cases of Richter's transformation in either arm.

CMV

Although no patients receiving chlorambucil had PCR-positive CMV with symptoms, 15.6% of patients receiving alemtuzumab had symptomatic CMV infections without end organ involvement. During the on-treatment period, 52.4% of patients receiving alemtuzumab and 7.5% of patients receiving chlorambucil had an asymptomatic positive CMV PCR result.

Among the 23 patients with symptomatic PCR-positive CMV infection, treatment was interrupted in 21; all but one received antivirals, and all recovered. Among 78 asymptomatic alemtuzumab patients who had one or more PCR-positive CMV results (including one post-treatment) treatment was interrupted in 47, and 36 received antivirals. Efficacy was maintained in alemtuzumab-treated patients with asymptomatic or symptomatic CMV PCR positivity. In patients with symptomatic CMV, ORR was 83% with 26% CR, and in patients with asymptomatic CMV, ORR was 92% with 29% CR. Median PFS for all PCR-positive CMV patients was 14.6 months, the same as for the entire treatment arm, and all recovered without sequelae.

DISCUSSION

Results from this study demonstrate the superiority of alemtuzumab compared with chlorambucil as first-line treatment for patients with CLL. Alemtuzumab treatment had a statistically significant longer PFS, higher ORR and CR, MRD-negative CRs, and longer time to alternative treatment, accompanied by a predictable and manageable safety profile. Currently, combinations with fludarabine, cyclophosphamide, and rituximab are considered to be the most active first-line therapies for CLL.[25-29] Alemtuzumab's high single-agent response rates seen in this study (24% CR, 59% partial response [PR]) compare favorably with those reported for fludarabine[5] (20% CR, 43% PR) and rituximab[30] (9% CR, 49% PR) monotherapy in similar patient populations, making alemtuzumab a good candidate for combination studies.

Other studies have suggested that alemtuzumab is active in patients with poor risk cytogenetics, such as deletions in 17 p or 11q, who usually do poorly with other therapies.[17-19] Alemtuzumab also eradicated MRD in some patients as previously reported.[8,20,21,31] The efficacy reported here with alemtuzumab supports the hypothesis that this agent is active in poor-risk patients. These results need to be confirmed by future clinical trials.

Our results also suggest that alemtuzumab in the first-line setting has an improved safety profile relative to that reported in more advanced disease. Infusion-related events were the most common AEs, were mild to moderate in severity and manageable, and decreased in frequency with subsequent doses. Recent studies have demonstrated that infusion-related events are reduced with subcutaneous administration of alemtuzumab.[22,32] The incidence of anemia, thrombocytopenia, febrile neutropenia, and symptomatic infections (other than CMV) were similar to chlorambucil, with infrequent use of colony-stimulating factors. Compared with the chlorambucil arm, more patients in the alemtuzumab arm who entered the study Coombs' positive converted to negative. There were no treatment-related deaths among patients treated with alemtuzumab. Both symptomatic CMV infections and asymptomatic CMV PCR positivity, which occurred more frequently with alemtuzumab, were successfully managed with standard therapies and did not appear to interfere with the ability to achieve a response to alemtuzumab. Guidelines for managing CMV reactivation in patients treated with alemtuzumab have been published previously.[33]

In the relapsed and refractory setting, combinations of alemtuzumab/fludarabine,[34,35] alemtuzumab/rituximab,[36,37] and cyclophosphamide/fludarabine/alemtuzumab/rituximab[38] have

shown promising results. Initial studies of alemtuzumab as maintenance[39] and consolidation therapy[20,31,40-43] are also encouraging. The high single-agent activity and manageable safety profile of alemtuzumab in this first-line study support further investigations in combination with other agents or as consolidation therapy to eliminate MRD.

Our results indicate that alemtuzumab may be the most active single agent for the treatment of patients with CLL, and appears to have an important role in the treatment of patients with poor-risk cytogenetics and in the eradication of MRD. The advent of improved risk-factor stratification, more sensitive and practical assays for detecting MRD, and treatment strategies that incorporate the most active agents, such as alemtuzumab, promise to lead to meaningful advances in the therapy of CLL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).