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Chronic lymphocytic leukemia patients with high-risk genomic features have inferior outcome on successive CALGB trials with alemtuzumab consolidation: subgroup analysis from CALGB 19901 and CALGB 10101

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Abstract

Alemtuzumab consolidation has been investigated to improve remission duration after fludarabine-based induction for chronic lymphocytic leukemia (CLL). The impact on genomic high-risk disease remains unknown. CALGB 19901 and 10101 enrolled previously untreated patients to receive alemtuzumab consolidation after fludarabine-based induction. Immunoglobulin heavy chain gene mutation status (IGHV) and interphase cytogenetics were assessed retrospectively. Treatment response with these alemtuzumab-containing regimens was similar, regardless of genomic risk, except for patients harboring del(17p), where few complete remissions were observed. PFS was similar between IGHV groups, but OS was inferior in IGHV unmutated patients ($P=0.03$). Cytogenetic risk group was associated with PFS and OS ($P=0.01$ for both), with

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Authorship

JJ and JB designed the present analysis. JJ drafted the manuscript and takes primary responsibility for the paper. JB, KR, TL, and RL were lead investigators for the original clinical trials. WZ and NH conducted the retrospective genetic studies. AR verified the data and conducted the statistical analysis with input from JJ and JB. All authors read and provided critique for the manuscript.

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Disclosures

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similarly short PFS in del(17p) and del(11q) and particularly short OS in del(17p) patients. Cytogenetic risk group remained significantly associated with PFS and OS when controlling for other prognostic factors (PFS: $P=0.009$; OS: $P=0.02$), as did the negative association of IGVH unmutated disease with OS ($P=0.004$). Results were similar when restricting to patients who received at least one dose of alemtuzumab consolidation, demonstrating limited ability to overcome the poor outcome associated with high-risk genetic features.

Keywords

CLL; alemtuzumab; clinical trial; cytogenetics; immunoglobulin genes

Introduction

Fludarabine-based chemoimmunotherapy prolongs both progression-free (PFS) and overall survival (OS) in previously untreated chronic lymphocytic leukemia (CLL) patients.¹⁻³ However, the majority of patients relapse within 5 years of completing primary therapy, and the outcome for patients with genomic high-risk disease – unmutated immunoglobulin heavy chain genes (IGVH) or karyotypic abnormalities such as del(17p13.1) and del(11q22.3) – remains poor.⁴⁻⁶ Consolidation therapy targeting eradication of residual disease following induction chemotherapy has been explored as a strategy to improve the likelihood and duration of first remission.

Alemtuzumab, a humanized monoclonal antibody targeting the CD52 antigen, has been shown to improve the quality of responses when employed in this context, and limited data suggest potential improvement in PFS.⁷⁻⁹ Additionally, studies in both relapsed CLL^{10,11} and also up-front therapy¹² have shown alemtuzumab yields response rates between 33-83% regardless of high-risk genomic features. However, whether the survival gap between those with and without high-risk genomic features can be closed with alemtuzumab has not been systematically addressed. The Cancer and Leukemia Group B (CALGB) has completed two phase 2 trials (CALGB 19901 and CALGB 10101) investigating alemtuzumab consolidation following fludarabine-based induction for previously untreated CLL.^{13,14} Primary analyses from both trials have been previously published, and we now report outcomes by genetic risk group.

Materials and Methods

Patients treated on CALGB 19901 received intravenous fludarabine 25 mg/m²/day for 5 consecutive days every 4 weeks for 4 months.¹³ After a two-month observation period, patients achieving CR, PR, or SD were eligible to receive consolidation with alemtuzumab at 30 mg/dose three times weekly for six weeks. Alemtuzumab was administered intravenously to the first 56 patients enrolled and subcutaneously (SC) to the remaining 29. Patients enrolled on CALGB 10101 received up to 6 cycles of induction therapy with fludarabine 25 mg/m² IV on days 1 to 5 of each cycle and rituximab 375 mg/m² on day 1 of cycles 2 through 6 after dose-escalation during cycle 1.¹⁴ Patients were observed for 3 months upon completion of induction and those with CR, PR, or SD proceeded to alemtuzumab 30 mg/dose SC 3 times weekly for 5 weeks after a one week dose escalation. All patients received prophylaxis for *Pneumocystis* and varicella. Institutional review-board approved, written informed consent was obtained from all patients participating in these studies.

Response was assessed according to the NCI CLL Working Group 1996 criteria.¹⁵ Progression-free survival (PFS) was defined as the time from registration until disease

progression or death from any cause, whichever came first, censoring those alive and progression-free at last follow-up. Overall survival (OS) was defined as the time from registration until death from any cause, censoring those alive at last follow-up.

Associations between baseline characteristics and IGVH status (mutated vs. unmutated) or cytogenetic risk groups as classified by Dohner¹⁶ (del(17p) vs. del(11q) vs. other) were compared using Fisher's Exact and Kruskal-Wallis tests for categorical and continuous variables, respectively. Estimated probabilities of PFS and OS were obtained using the Kaplan-Meier method, and the log-rank test evaluated differences between survival curves. Multivariable analyses using a limited backward selection procedure were conducted for PFS and OS to control for other prognostically important covariates, including age, sex, white blood count (WBC), Rai stage (III/IV vs I/II), and performance status (1/2 vs 0). Analyses were also conducted according to cytogenetic risk group. All models adjusted for study (CALGB 10101 vs. 19901), but this retrospective subgroup analysis was not designed to compare the different induction regimens employed in these studies. Data were locked as of October 2011. All analyses were performed by the Alliance for Clinical Trials in Oncology Statistics and Data Center.

Results

A total of 187 CLL patients were enrolled on protocols 19901 (n=85) or 10101 (n=102). Baseline genetic data was available for 150 (80%) of the enrolled patients: there were results for both FISH and IGVH mutational status for 103 (55%), FISH only for 23 (12%), IGVH only for 24 (13%), and no genetic information in 37 patients (20%). Among the patients with a genetic result, baseline characteristics did not differ significantly between IGVH mutated (n=37) and IGVH unmutated patients (n=90), nor did they differ among patients with del(17p) (n = 9), del(11q) (n = 27), and those without these poor-risk cytogenetics (n = 90) (Table 1).

The proportion of patients who began treatment with alemtuzumab consolidation also did not differ significantly between IGVH mutated and unmutated groups (70% vs. 60%, $P=0.32$), nor across the cytogenetic risk groups (del(17p) 56% vs. del(11q) 48% vs. not del(17p)/del(11q) 67%, $P=0.20$). Treatment response, with or without alemtuzumab consolidation, was similar between patients with and without IGVH mutations ($P=0.86$) but tended to differ across cytogenetic risk groups ($P=0.06$) (Table 1). In particular only 2 of 9 patients with del(17p) achieved CR with these regimens (22%), as opposed to 56% of del(11q) patients and 41% of patients without either of these genetic aberrations.

With a median follow-up of 55 months for those progression-free, there was no significant difference in PFS by IGVH status, with estimated medians of 27 (95%CI: 18-32) and 21 (95%CI: 13-33) months, respectively, in the unmutated and mutated groups ($P=0.87$) (Table 1, Figure 1A). In spite of similar PFS, OS was significantly shorter in the IGVH unmutated group with a median of 68 months (95%CI: 61-85) compared to the IGVH mutated group where the median has not been reached ($P=0.03$) (Table 1, Figure 1B), suggesting that IGVH mutated patients fare better with salvage therapy upon relapse. The relationship between IGVH mutated and unmutated patients with respect to PFS and OS did not change when restricted to those patients who received at least one dose of alemtuzumab consolidation (Figures 1C,1D).

In contrast, almost all patients with either del(17p) or del(11q) had progressed within 48 months of going on study (Figure 2A). Among the 9 patients with del(17p), all but one had progressed between 4.1 and 50.1 months. One patient treated on CALGB 10101 had not progressed at 38.2 months. Considering the 27 patients with del(11q), all but two had

progressed, most between 2.1 and 42.9 months of follow-up. The two patients not progressing were censored at 27 and 48 months; the former patient was diagnosed with colon cancer and succumbed to the disease 12 months later, and the latter was still progression-free and alive at last follow-up. Hence, PFS was shorter for patients with either del(17p) or del(11q), relative to those without these genetic aberrations, with estimated medians of 26 months (95% CI: 4-43), 27 months (95% CI: 17-29), and 33 months (95% CI: 29-39), respectively ($P=0.01$, Table 1). With respect to OS, there remained a significant difference in clinical outcome across the cytogenetic risk groups ($P=0.01$, Table 1, Figure 2B), where the shortest OS was in patients with del(17p) with an estimated median of 38 months (95%CI: 15-not estimated (NE)), followed by patients with del(11q) with an estimated median survival of 65 months (95% CI: 45-111), and the longest OS durations were in patients without these two aberrations, with an estimated median survival of 93 months (95% CI: 79-NE). When restricting the analysis to those who had received at least one dose of alemtuzumab consolidation, similar results were observed (Figures 2C-2D).

When controlling for other prognostic variables, IGVH mutation status continued to demonstrate no association with PFS (hazard ratio (HR) 1.09, 95%CI: 0.69-1.71, $P=0.72$), and OS remained significantly inferior among unmutated patients ($P=0.004$), particularly beyond 36 months of follow-up (HR post 36 months 5.78, 95%CI: 2.02-16.60) (Table 2). Cytogenetic risk group remained significantly associated with PFS ($P=0.009$), where the risk of an event tended to be higher in patients with del(17p) (HR 1.96, 95% CI: 0.92-4.16) or del(11q) (HR 2.06, 95% CI: 1.25-3.38) relative to patients without these cytogenetic aberrations. Similarly, differences were observed with respect to OS ($P=0.02$), where patients with del(17p), and to a lesser extent, those with del(11q) tended to have a higher risk of death than those patients without these aberrations (HR 3.68, 95% CI: 1.47-9.17 and HR 1.58, 95% CI: 0.85-2.96, respectively).

Since the availability of genetic risk information could have potentially introduced selection biases influencing these results, we compared characteristics among the various groups of patients included or excluded in the analyses, i.e. patients with both FISH and IGVH mutational status ($n = 103$), patients with FISH results only ($n=23$), patients with IGVH results only ($n=24$), and patients with neither result ($n=37$). Notably, 92% of the patients with only an IGVH result were treated on CALGB 19901 and induced with single-agent fludarabine compared with about 40% in the other patient groups ($P<0.0001$). This group of patients had a much lower response rate and shorter PFS compared to the other patient groups, although OS was not significantly different among them ($P=0.65$). Thus, the IGVH analyses included a group of poor prognosis patients that was not included in the FISH analyses and also tended to exclude patients with better clinical outcomes.

Discussion

Prior studies have suggested that the addition of alemtuzumab consolidation after fludarabine-based induction therapy can potentially improve not only treatment response rates but progression-free survival, as well. However, these conclusions are largely based on the results of a single randomized phase 3 study in which only 11 of 21 evaluable patients received alemtuzumab consolidation.⁹ While that study demonstrated a statistically significant improvement in 3-year PFS after alemtuzumab (90.9% versus 40%), an impact on overall survival was not reported. Further, while the benefits were said to extend to all patients without respect to genetic risk status, the authors report that the single early progressor after alemtuzumab was a patient with unmutated IGVH and del(11q) cytogenetics.⁸

Remission quality has been associated with longer remission duration in some prior studies. Our results suggest that alemtuzumab may indeed improve treatment response, since overall response rates were similar across genetic risk groups, with the notable exception of del(17p) patients, at the conclusion of induction and consolidation, which has not been observed after either fludarabine or rituximab-fludarabine induction alone. Further, in our study population, patients with unmutated IGVH experienced similar PFS versus patients with the mutated phenotype. This suggests that the expected gap in PFS between these groups could potentially be closed with alemtuzumab consolidation. However, as noted above, a group of patients induced with single agent fludarabine, which previous studies have suggested is inferior to regimens containing chemotherapy and monoclonal antibody, was included in the IGVH analysis; better prognosis patients were excluded. Thus, the apparent minimization in the gap in PFS, may be due to selection bias. It is also possible that the excluded patients with better outcomes had IGVH mutated disease, thus resulting in lower PFS estimates for the mutated group. Ultimately, however, patients with unmutated IGVH still demonstrated inferior overall survival, the outcome we would most like to influence.

When outcomes were considered according to cytogenetic features (del(17p), del(11q), or neither del(17p)/del(11q)), both high-risk abnormality groups, del(17p) and del(11q), continued to demonstrate inferior PFS, and particularly del(17p), inferior OS. While the absence of a comparator group not receiving alemtuzumab consolidation limits our ability to draw definitive conclusions, these results suggest that if there is a survival benefit attributable to regimens containing alemtuzumab consolidation among genetically high-risk patients, the benefit is likely modest.

Our study represents the largest analysis to yet consider the utility of alemtuzumab consolidation among patients with high-risk CLL. We recognize that in the absence of a randomized trial comparing regimens with and without alemtuzumab consolidation, one cannot fully determine the degree to which the gap in PFS or OS may have been diminished between high and low-risk patients. However, this will likely prove to be the first and potentially only study addressing the important question of whether alemtuzumab consolidation can neutralize the inherent risk defined by genetic features like del(17p) or unmutated IGVH. In our study population, the unfavorable prognostic impact of poor-risk cytogenetics, particularly del(17p), on both PFS and OS remained with alemtuzumab consolidation, suggesting that any possible benefit would have been small. Despite potential improvement in PFS with respect to IGVH status, a statistically significant inferior OS was still observed for patients with unmutated disease.

The modest clinical benefit described here must be weighed against the reported potential for life-threatening infectious toxicity during and following alemtuzumab consolidation. Alemtuzumab consolidation was associated with an unexpectedly high rate of mortality due to infection on CALGB 10101, and the only previous trial to suggest a possible PFS benefit after consolidation (German CLL Study Group CLL4B) was suspended early due to unacceptable infectious complications.^{9,14} Outcomes for these challenging groups of patients remain poor, thus consolidation and maintenance strategies remain appealing. However, our experience with alemtuzumab suggests that other active agents, such as kinase inhibitors (dinaciclib, idelasib, ibrutinib) or immunomodulatory drugs (lenalidomide), might be more safely and effectively exploited in this context.

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Figure 1A.

Kaplan-Meier estimates of progression-free survival (PFS) by immunoglobulin heavy chain variable region (IGVH) mutational status (unmutated = solid line, mutated = dashed line).

Figure 1B.

Kaplan-Meier estimates of overall survival (OS) by IGVH mutational status (unmutated = solid line, mutated = dashed line).

Figure 1C.

Kaplan-Meier estimates of progression-free survival (PFS) by immunoglobulin heavy chain variable region (IGVH) mutational status (unmutated = solid line, mutated = dashed line) in patients receiving alemtuzumab consolidation.

Figure 1D.

Kaplan-Meier estimates of overall survival (OS) by IGVH mutational status (unmutated = solid line, mutated = dashed line) in patients receiving alemtuzumab consolidation.

Figure 2A.

Kaplan-Meier estimates of PFS by cytogenetic risk group [del(17p13.1) = solid line, del(11q22.3) = dashed line, Not del(17p13.1)/del(11q22.3) = dotted line].

Figure 2B.

Kaplan-Meier estimates of OS by cytogenetic risk group [del(17p13.1) = solid line, del(11q22.3) = dashed line, Not del(17p13.1)/del(11q22.3) = dotted line].

Figure 2C.

Kaplan-Meier estimates of PFS by cytogenetic risk group [del(17p13.1) = solid line, del(11q22.3) = dashed line, Not del(17p13.1)/del(11q22.3) = dotted line] in patients receiving alemtuzumab consolidation.

Figure 2D.

Kaplan-Meier estimates of OS by cytogenetic risk group [del(17p13.1) = solid line, del(11q22.3) = dashed line, Not del(17p13.1)/del(11q22.3) = dotted line] in patients receiving alemtuzumab consolidation.

Figure 3A.

Kaplan-Meier estimates of progression-free survival (PFS) according to availability of genetic risk stratification data: none, FISH only, both IGVH and FISH, IGVH only.

Figure 3B.

Kaplan-Meier estimates of overall survival (OS) according to availability of genetic risk stratification data: none, FISH only, both IGVH and FISH, IGVH only.

Table 1

Patient characteristics and treatment outcome by genetic risk group.

	IGVH Mutated n=37	IGVH Unmutated n=90	P	Not del(17p)/del(11q) n=90	del(11q) n=27	del(17p) n=9	P
Study, no. (%)							
CALGB 19901 (F A)	21 (57)	42 (47)	0.33	38 (42)	9 (33)	3 (33)	0.71
CALGB 10101 (FR A)	16 (43)	48 (53)		52 (58)	18 (67)	6 (67)	
Age, (years)			0.16				0.74
Median	58	55		58	58	57	
Range	44-81	34-81		34-81	35-81	51-65	
Sex, no. (%)			0.07				0.17
Male	24 (65)	73 (81)		66 (73)	21 (78)	4 (44)	
Female	13 (35)	17 (19)		24 (27)	6 (22)	5 (56)	
White blood count, $\times 10^9/L$			0.36				0.81
Median	73.7	100		6.3-402.0	98.9	46.9	
Range	6.3-465.6	13.9-669.0			12.0-669.0	28.0-235.0	
ECOG Performance Status, no. (%)			0.84				0.9
0	22 (59)	56 (62)		59 (66)	16 (59)	6 (67)	
2-Jan	15 (41)	34 (38)		31 (34)	11 (41)	3 (33)	
Rai Stage, no. (%)			1				0.27
I/II	27 (73)	66 (73)		63 (70)	22 (81)	5 (56)	
III/IV	10 (27)	24 (27)		27 (30)	5 (19)	4 (44)	
Received Alemtuzumab, no. (%)			0.32				0.2
No	11 (30)	36 (40)		30 (33)	14 (52)	4 (44)	
Yes	26 (70)	54 (60)		60 (67)	13 (48)	5 (56)	
Overall Response, no. (%)			0.86				0.06
CR	12 (32)	37 (41)		37 (41)	15 (56)	2 (22)	
PR	16 (43)	34 (37)		42 (47)	7 (26)	4 (44)	
SD	5 (14)	11 (12)		5 (6)	4 (15)	3 (33)	

	IGHV Mutated n=37	IGHV Unmutated n=90	P	Not del(17p)/del(11q) n=90	del(11q) n=27	del(17p) n=9	P
PD/NE	4 (11)	9 (10)		6 (7)	1 (4)	0 (0)	
Progression-Free Survival (PFS)			0.87				0.01
Median, months (95% CI)	21 (13-33)	27 (18-32)		33 (27-39)	27 (17-29)	26 (4-43)	
PFS at 36 months, % (95% CI)	30 (16-46)	33 (24-43)		44 (33-54)	20 (7-37)	33 (8-62)	
Overall Survival (OS)			0.03				0.01
Median, months (95% CI)	NR	68 (61-85)		93 (79-NE)	65 (45-111)	38 (15-NE)	
OS at 36 months, % (95% CI)	75 (58-86)	82 (73-89)		83 (74-89)	89 (69-96)	56 (20-80)	

Key: F= fludarabine; A = alemtuzumab; R = rituximab; Cyto = interphase cytogenetics; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; CI = confidence interval; NR = not reached.

Multivariable Models for progression-free survival and overall survival according to IGVH mutational status or presence of poor-risk cytogenetics.

Table 2

Models including IGVH Mutational Status						
Variable	Progression-Free Survival			Overall Survival		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
IGVH unmutated vs mutated [†]						
Prior to 3 years	1.09	0.69-1.71	0.72	0.81	0.36-1.84	0.004
Following 3 years				5.78	2.02-16.60	
CALGB 10101 vs. 19901	0.60	0.40-0.92	0.02	0.54	0.30-0.96	0.04
Female vs male	1.62	1.02-2.58	0.04	--	--	--
WBC, 2-fold increase	1.42	1.19-1.70	<0.001	--	--	--
Age, 10-year increase	--	--	--	1.53	1.17-1.99	0.002

Models including Cytogenetic Risk Group					
Cytogenetic risk group					
del(17p) vs. not	1.96	0.92-4.16	0.009	3.68	1.47-9.17
del(17p)/del(11q)	2.06	1.25-3.38		1.58	0.85-2.96
del(11q) vs. not					
del(17p)/del(11q)					
CALGB 10101 vs. 19901	0.83	0.54-1.27	0.38	0.83	0.44-1.55
					0.55
WBC, 2-fold increase	1.37	1.17-1.61	<0.001	--	--

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, WBC=white blood count
Hazard ratios prior to 3 years and following 3 years are reported.

[†] IGVH status grossly violated the proportional hazards assumption in the overall survival model.