Impact of Age on Outcomes After Initial Therapy With Chemotherapy and Different Chemoimmunotherapy Regimens in Patients With Chronic Lymphocytic Leukemia: Results of Sequential Cancer and Leukemia Group B Studies

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ABSTRACT

Purpose

Chronic lymphocytic leukemia (CLL) is a disease of the elderly, yet few clinical trials include a significant number of older patients, and outcomes after specific therapies can be different depending on age.

Patients and Methods

We examined patients enrolled onto successive first-line CALGB CLL trials to determine whether efficacy of regimens varied by age, focusing on ideal chemotherapy choice and benefit of immunotherapy addition to chemotherapy in older patients. Regimens included chlorambucil, fludarabine, fludarabine plus rituximab (FR), fludarabine with consolidation alemtuzumab, and FR with consolidation alemtuzumab.

Results

A total of 663 patients were evaluated for response, progression-free survival (PFS), and overall survival (OS) by age group. Interaction effects of fludarabine versus chlorambucil by age group (PFS, $P = .046$; OS, $P = .006$) showed that among patients younger than 70 years, PFS and OS was improved with fludarabine over chlorambucil (PFS: hazard ratio [HR] = 0.6, 95% CI, 0.5 to 0.8; OS: HR = 0.7, 95% CI, 0.5 to 0.9), but not in older adults (PFS, HR = 1.0, 95% CI, 0.6 to 1.7; OS: HR = 1.5, 95% CI, 0.9 to 2.3). In contrast, FR improved outcomes relative to fludarabine, irrespective of age (PFS: HR = 0.6, 95% CI, 0.4 to 0.7; OS: HR = 0.7, 95% CI, 0.5 to 0.9). Alemtuzumab consolidation did not provide benefit over similar regimens without alemtuzumab ($P > .20$), irrespective of age.

Conclusion

These data support the use of chlorambucil as an acceptable treatment for many older patients with CLL and suggest rituximab is beneficial regardless of age. These findings bear relevance to both routine care of CLL patients 70 years and older and also future clinical trials in this population.

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INTRODUCTION

CLL is a disease of the elderly, with a median age at diagnosis of 72 years and most patients diagnosed after age 65.^{1,2} Therapy in this population must carefully balance efficacy and tolerability, as older patients are likely to have diminished organ function and significant comorbid medical conditions.³ Despite the advanced age of the majority of patients with CLL, older adults are underrepresented in clinical trials. In the phase III trials that have shown superiority of fludarabine to chlorambucil⁴ and fludarabine plus cyclophosphamide to fludarabine^{5,6} or chlorambucil⁵ alone, median ages were in the

early 60s. In the large studies that have demonstrated the superiority of chemoimmunotherapy in this disease, median ages were between 58 and 64 years.⁷⁻⁹ It is therefore quite difficult to know whether results of these pivotal studies are applicable to the majority of CLL patients who are substantially older than the study participants.

Few studies have been undertaken to look specifically at initial therapy for older CLL patients. The German CLL5 study, which examined fludarabine versus chlorambucil as single agents, showed improved overall response rate (ORR) with fludarabine; however, no difference in progression-free survival (PFS) or overall survival (OS) was seen. In

fact, OS, although not statistically significantly different, trended toward favoring chlorambucil.¹⁰ Although chemoimmunotherapy with fludarabine and rituximab (FR) or fludarabine, cyclophosphamide, and rituximab (FCR) have become standard for younger patients with CLL, limited analysis of outcome of patients older than 69 years demonstrated lower response rates and increased toxicity.¹¹ Two groups have examined the combination of chlorambucil plus rituximab in untreated older patients^{12,13} showing promising activity with a tolerable safety profile, with one study showing improved ORR and PFS compared with matched historic controls treated with chlorambucil alone.¹² Certainly these studies argue that the optimal frontline therapy for older patients with CLL is still under debate. To address this question and guide future research, we have analyzed outcomes of older patients enrolled on frontline CALGB trials.

PATIENTS AND METHODS

Patients, Treatment Regimens, and Definitions of Clinical End Points

Patients enrolled on the successive frontline Cancer and Leukemia Group B (CALGB) studies 9011,⁴ 9712,⁷ 19901,¹⁴ and 10101¹⁵ were included in this analysis. All patients participating in these institutional review board–approved clinical studies signed written informed consent. Treatment regimens examined include chlorambucil (Ch) on CALGB 9011⁴ ($n = 41 \geq 70$, $n = 152 < 70$ years), fludarabine alone on CALGB 9011⁴ ($n = 46 \geq 70$, $n = 133 < 70$ years), FR on CALGB 9712⁷ ($n = 24 \geq 70$, $n = 80 < 70$ years), fludarabine with alemtuzumab consolidation (FA) on CALGB 19901¹⁴ ($n = 16 \geq 70$, $n = 69 < 70$ years), and FR with alemtuzumab consolidation (FRA) on CALGB 10101¹⁵ ($n = 21 \geq 70$, $n = 81 < 70$ years). CALGB 9011 was the only randomized phase III trial, whereas CALGB 19901, 9712, and 10101 were phase II clinical trials. Patients were assessed for response using the 1996 National Cancer Institute Working Group response criteria,¹⁶ with ORR including achievement of complete and partial responses. PFS was defined as the time from registration/randomization until disease progression or death, whichever came first. Nine patients were not adequately observed for PFS and were excluded from these analyses, and 37 patients (6%) died at least 3 months after the date last known to be progression-free and were censored for PFS at date last evaluated. OS was defined as the time from randomization until death from any cause.

Statistical Analysis

Pretreatment demographic and clinical characteristics across the treatment groups were compared using Pearson's χ^2 test or the Kruskal-Wallis test. ORR of the treatment groups are provided with exact Clopper-Pearson 95% CIs. Estimates of PFS and OS were obtained by the Kaplan-Meier method. The primary pairwise treatment comparisons included (1) fludarabine versus Ch, (2) FA versus fludarabine, (3) FR versus fludarabine, and (4) FRA versus FA. Influence of treatment regimen on response rates was evaluated using logistic regression models, whereas PFS and OS differences were compared using the proportional hazards model, controlling for age (> 70 v < 70 years), sex (female v male), log-transformed WBC count, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and stage of disease (0/I/II v III/IV); stage of disease was a stratification factor in the OS model as it showed departures from the proportional hazards assumption in diagnostic plots and when tested by a time-dependent covariate expressed as the product of disease stage and the log of survival time ($P = .001$). For each of the primary treatment comparisons, models were fit including an interaction term between treatment regimen and age and controlled for the same variables listed previously. P values were obtained for the interaction term, and hazard ratio estimates with 95% CIs comparing treatment regimens are presented by age group. All tests were two-sided, and statistical significance was declared at $\alpha = .05$. No attempt was made to adjust for multiple comparisons, as these estimates obtained and trends observed were intended to provide valuable information

and guidance for planning future studies. All analyses were performed by the Alliance for Clinical Trials in Oncology Statistics and Data Center. Follow-up data on all patients were current as of October 2011.

RESULTS

We examined ORR, PFS, and OS among the five different treatment regimens included in four successive CALGB CLL trials with a median follow-up for OS across all studies of 92 months (range, 16 to 237 months). Baseline characteristics for all studies are outlined in Table 1. There were no significant differences among the treatment arms in terms of age (≥ 70 v < 70 years), sex, Rai stage (intermediate v high), and baseline WBC count. Baseline creatinine clearance (CrCl) was found to be significantly different between younger and older patients (median, 55.68 mL/min/1.73 m² v 81.72 mL/min/1.73 m², $P < .001$); however, CrCl in patients age 70 years and older were not significantly different among the treatment regimens ($P = .40$).

ORR was significantly different among the treatment regimens (Table 2), with the lowest ORR seen in patients treated with chlorambucil (ORR, 37%; 95% CI, 0.30 to 0.44). ORR was improved in patients treated with fludarabine (ORR, 60%; 95% CI, 0.53 to 0.68) and further improved with FR (ORR, 84%; 95% CI, 0.75 to 0.90). ORR was not substantially higher with alemtuzumab consolidation when compared with response rates achieved on similar regimens without alemtuzumab consolidation. In a multivariable analysis, treatment regimen as well as ECOG PS ($P = .03$), sex ($P < .001$) and Rai stage ($P < .001$) were significantly associated with response, whereas WBC count was moderately associated ($P = .06$), and age group was not a significant predictor of response ($P = .56$). Furthermore, there was no indication that the effect of treatment regimen on ORR varied according to age group ($P = .87$).

When looking at PFS within each of the age groups (< 70 v ≥ 70 years), significant differences were seen among the treatment regimens ($P < .001$; Table 3). Rituximab-containing regimens yielded the highest PFS estimates. (Fig 1A, 1b). In a multivariable model controlling for age and other potentially prognostic variables, fludarabine induced significantly longer PFS over chlorambucil (HR = 0.68; 95% CI, 0.5 to 0.9). However, there was a significant interaction between treatment regimen and age group with respect to PFS ($P = .046$), with age group acting as an effect modifier. In the age less than 70 years cohort ($n = 128 + 138$), the risk of progression when treated with fludarabine decreased 40% compared with those treated with Ch (HR = 0.60; 95% CI, 0.46 to 0.78); however, in the ≥ 70 years cohort ($n = 46 + 38$), the estimated risk of progression with fludarabine was not different compared with that of Ch (HR = 1.04; 95% CI, 0.65 to 1.65; Fig 1C). In contrast, the addition of rituximab to fludarabine decreased the risk of progression by 44% relative to fludarabine alone (HR = 0.56; 95% CI, 0.43 to 0.74; $P < .001$) and did not have a differential effect on PFS by age group ($P = .55$; Fig 1D). Inclusion of alemtuzumab consolidation did not improve PFS over like regimens without alemtuzumab (FA v F: HR = 0.92, 95% CI, 0.70 to 1.22, $P = .59$; and FRA v FR: HR = 1.01, 95% CI, 0.73 to 1.41, $P = .95$), and there were no significant interactions between treatment and age for these two comparisons ($P = .66$ and $P = .19$; Fig 1E, 1F).

OS was found to be significantly different across the treatment regimens for patients younger than age 70 years ($P < .001$), but not for the patients ≥ 70 years of age ($P = .13$; Table 3, Figs 2A and 2B). As in

Table 1. Baseline Characteristics

Characteristic	Total (N = 663)		F (n = 179)		Ch (n = 193)		FA (n = 85)		FR (n = 104)		FRA (n = 102)		P
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Age, years													.71
< 70	515	78	133	74	152	79	69	81	80	77	81	79	
≥ 70	148	22	46	26	41	21	16	19	24	23	21	21	
Age for patients < 70 years													.02
Median	58		60		59		53		60		56		
Range	34-69		37-69		35-69		40-69		36-69		34-69		
Age for patients ≥ 70 years													.20
Median	74		74		74		72		74		75		
Range	70-88		70-87		70-88		70-78		70-86		71-81		
Sex													.50
Male	473	71	128	72	130	67	60	71	80	77	75	74	
Female	190	29	51	28	63	33	25	29	24	23	27	26	
Rai stage													.19
0/I/II	416	63	109	61	114	59	59	69	62	60	72	71	
III/IV	247	37	70	39	79	41	26	31	42	40	30	29	
Performance status													.96
0	399	62	111	63	113	62	53	62	60	58	62	61	
1	221	34	56	32	60	33	30	35	38	37	37	36	
2/3	27	4	8	5	9	5	2	2	5	5	3	3	
WBC count													.73
Median	76.9		77.3		72.4		80.7		83.1		81.5		
Range	5.5-709.0		9.2-709.0		8.0-588.0		5.5-669.0		8.8-436.0		6.3-409.0		

Abbreviations: Ch, chlorambucil; F, fludarabine; FA, fludarabine with alemtuzumab consolidation; FR, fludarabine and rituximab; FRA, fludarabine and rituximab with alemtuzumab consolidation.

the PFS analysis, age group modified efficacy differences for fludarabine versus Ch ($P = .006$). Among younger patients, the risk of death when treated with fludarabine decreased by 31% compared with the risk when treated with Ch (HR = 0.69; 95% CI, 0.53 to 0.90). Although not reaching statistical significance, the risk of death in older patients was estimated to be 45% higher when treated with fludarabine versus Ch (HR = 1.45; 95% CI, 0.92 to 2.28; Fig 2C). No significant difference in the cause of death (related or unrelated to CLL) was observed between patients receiving fludarabine and Ch (Appendix Table A1, online only). Thus different causes of death between treatment groups was unlikely to significantly impact the OS results. Similar to what was observed with PFS, the addition of rituximab to fludarabine improved OS among all patients, with the risk of death decreasing an estimated 35% with rituximab (HR = 0.65; 95% CI, 0.49 to 0.87, $P = .004$). This improvement was not dependent on age

($P = .96$; Fig 2D). As was seen with PFS, there was little OS benefit to the addition of alemtuzumab consolidation (FA ν F: HR = 0.82, 95% CI, 0.60 to 1.12, $P = .22$; FRA ν FR: HR = 0.92, 95% CI, 0.59 to 1.44, $P = .72$), with no significant interaction between treatment and age for either FA versus fludarabine or FRA versus FR ($P = .31$ and $P = .34$, respectively; Figs 2E and 2F).

DISCUSSION

Here we report a comprehensive analysis of older patients enrolled on frontline CALGB trials with the primary goal of examining the impact of current therapies for CLL. Our data show that although response rates are improved, fludarabine does not confer significant benefit in PFS nor OS to adults ≥ 70 years, similar to what was shown in the

Table 2. Response Rates Among Treatment Regimens and According to Age Group

Treatment Regimen	Study	All Patients		Age < 70 Years		Age ≥ 70 Years	
		%	95% CI	%	95% CI	%	95% CI
F	CALGB 9011	60	53 to 68	58	48 to 68	63	51 to 74
Ch	CALGB 9011	37	30 to 44	35	26 to 45	39	28 to 52
FA	CALGB 19901	72	61 to 81	76	63 to 86	61	39 to 80
FR	CALGB 9712	84	75 to 90	82	70 to 91	85	72 to 94
FRA	CALGB 10101	90	83 to 95	89	79 to 95	92	79 to 98

NOTE. Exact Clopper-Pearson 95% CIs are reported in parentheses.

Abbreviations: Ch, chlorambucil; F, fludarabine; FA, fludarabine with alemtuzumab consolidation; FR, fludarabine and rituximab; FRA, fludarabine and rituximab with alemtuzumab consolidation.

Table 3. Multivariable Analysis for Progression-Free Survival and Overall Survival Comparing Treatment Regimens Overall and by Age

Treatment Comparison	Age Group (years)	Progression-Free Survival				Overall Survival			
		No.	Hazard Ratio*	95% CI	P†	No.	Hazard Ratio*	95% CI	P†
F v Ch	All ages	350	0.68	0.55 to 0.86	.0009	357	0.84	0.67 to 1.05	.13
	< 70	266	0.60	0.46 to 0.78	.046	273	0.69	0.53 to 0.90	.006
	≥ 70	84	1.04	0.65 to 1.65		84	1.45	0.92 to 2.28	
FA v F	All ages	259	0.92	0.70 to 1.22	.59	260	0.82	0.60 to 1.12	.22
	< 70	197	0.92	0.67 to 1.27	.66	198	0.78	0.54 to 1.12	.31
	≥ 70	62	1.07	0.59 to 1.93		62	1.11	0.62 to 2.01	
FR v F	All ages	275	0.56	0.43 to 0.74	< .001	276	0.65	0.49 to 0.87	.004
	< 70	206	0.59	0.43 to 0.81	.55	207	0.64	0.46 to 0.91	.96
	≥ 70	69	0.49	0.28 to 0.84		69	0.65	0.39 to 1.10	
FRA v FR	All ages	199	1.01	0.73 to 1.41	.95	199	0.92	0.59 to 1.44	.72
	< 70	155	1.15	0.79 to 1.66	.19	155	1.08	0.64 to 1.82	.34
	≥ 70	44	0.67	0.32 to 1.38		44	0.66	0.28 to 1.57	

NOTE. Models included treatment regimen, age group, sex, log-transformed WBC count, performance status, and Rai stage with or without the interaction of treatment regimen and age group. All models for overall survival used Rai stage as a stratification factor because of the strong violation of proportional hazards for this variable.

Abbreviations: Ch, chlorambucil; F, fludarabine; FA, fludarabine with alemtuzumab consolidation; FR, fludarabine and rituximab; FRA, fludarabine and rituximab with alemtuzumab consolidation.

*A hazard ratio > 1 (< 1) indicates a greater (lesser) risk of an event for the first category listed in the treatment comparison.

†The *P* values in the rows labeled "All ages" are from pairwise tests of treatment main effects, whereas the *P* values in the rows by age group are from tests of treatment by age group interaction effects.

German CLL5 study.¹⁰ The discrepancy between ORR and PFS is driven by patients ≥ 70 years treated with chlorambucil, in whom PFS estimates did not differ largely between nonresponding and responding patients (summarized in Appendix Table A2), potentially due to the number of patients in this age group with stable disease. Furthermore, similar to the CLL5 study,¹⁰ we have shown a trend toward poorer OS with fludarabine versus chlorambucil in this subgroup of patients. In contrast, the addition of rituximab to fludarabine-containing regimens significantly improves both PFS and OS in younger and older patients, showing the importance of this agent in the current frontline CLL regimens. At the time of this analysis, the addition of consolidation alemtuzumab did not improve outcomes in either younger or older patients, although these data are relatively immature in comparison with those of the older studies. Collectively, these data suggest that rituximab should be included in future trials designed for older patients with CLL.

An additional consideration in choosing initial therapy for older patients with CLL is the balance between tolerability and efficacy. Older patients are particularly susceptible to toxicity associated with chemotherapy, likely due to physiologic decline in renal function. Forty-four percent of patients older than 65 years have some degree of chronic kidney disease,¹⁷ which increases the likelihood for toxicity with renal-cleared agents such as fludarabine and cyclophosphamide. In this analysis, CrCl in patients ≥ 70 years of age was not significantly different among the treatment regimens, so it is unlikely that differences observed in outcomes among treatment regimens is confounded by changes in renal function, except as related to individual drug clearance. Likely related to toxicity, it has been reported that many older adults do not complete the entire prescribed course of fludarabine therapy,¹¹ which may influence PFS and OS. In the data derived from CALGB 9011, there was no significant difference in the number of cycles of therapy received between those treated with chlorambucil and fludarabine within the younger and older age groups (Appendix Table A3, online only), though it is possible that

individual patients may have had therapy interrupted or discontinued because of toxicity. It has been argued that perhaps fludarabine given at a lower dose would be more tolerable and thus effective. Fludarabine has been examined on a 3-day schedule of 30 mg/m² (compared with a 5-day schedule of 25 mg/m²) in previously treated CLL with results comparable to those of historical controls¹⁸ and is currently being evaluated by the German CLL Study Group in untreated disease (clinical trials identifier NCT00281892). Poor tolerability of therapy, in addition to the relatively small number of patients treated in the phase II setting, may as well contribute to the lack of efficacy seen with consolidation alemtuzumab. In CALGB 19901 and 10101, 63% of patients received any consolidation alemtuzumab, and approximately half of the patients enrolled on the two studies completed therapy per protocol. In contrast, rituximab, which is a generally well-tolerated therapy, showed significant benefit in both younger and older patients.

Although we attempted to control for many variables across trials in this retrospective study by reviewing the original data extensively and using multivariable analysis to control for important patient characteristics, the inherent differences among these trials is a limitation to our analysis. Only one of the trials examined was a phase III trial comparing randomized arms (CALGB 9011). The data span two decades, and differences in supportive care during this time may contribute to superior outcomes in the later studies. Additionally, molecular features such as interphase cytogenetics, immunoglobulin heavy chain variable region mutational status, and *TP53* mutations were not examined, as they were not available from all the trials. To date, no study has shown a difference in these prognostic factors by age group, thereby diminishing the probability that imbalances in these features explain the observed results. Newer studies performed by the German CLL Study Group have used functional scores to assign therapy based on physiologic versus chronologic age. Although functional studies were not performed in patients in these different studies, future investigation should prospectively validate these. In addition, elderly

Fig 1. Kaplan-Meier curves for progression-free survival (PFS) by treatment regimen and by age: (A) across treatment regimens in patients younger than 70 years (F, n = 131; Ch, n = 145; FA, n = 69; FR, n = 80; FRA, n = 81), (B) across treatment regimens in patients ≥ 70 years (F, n = 46; Ch, n = 41; FA, n = 16; FR, n = 24; FRA, n = 21), (C) F versus Ch by age, (D) F versus FR by age, (E) F versus FA by age, and (F) FR versus FRA by age. In A-B, median PFS estimates are provided in parentheses for each treatment regimen, and the *P* values were calculated using the log-rank test. The interaction *P* values in C-F were obtained from a proportional hazards model using Wald tests. Ch, chlorambucil; F, fludarabine; FA, fludarabine with alemtuzumab consolidation; FR, fludarabine with rituximab; FRA, FR with alemtuzumab consolidation.

CLL studies in which comorbidities may contribute to non-CLL related mortality should consider prospective determination of impact of non-CLL, non-treatment-related deaths in survival determination.

This analysis was performed using the age cutoff of 70 years, as has been used in other retrospective analyses of frontline therapy in CLL.^{11,19} The German CLL5 study, however, used 65 years as the

discriminator between older and younger patients, so we performed outcomes analyses of fludarabine versus chlorambucil at 65 years as well. With this cut point, we did not observe a significant difference in the relationship between treatment and PFS according to age group (interaction *P* = .38; Fig 3A). Here, PFS was improved to a similar extent for fludarabine versus chlorambucil in both the group of

Fig 2. Kaplan-Meier curves for overall survival (OS) by treatment regimen and by age: (A) across treatment regimens in patients younger than 70 years (F, $n = 133$; Ch, $n = 152$; FA, $n = 69$; FR, $n = 80$; FRA, $n = 81$), (B) across treatment regimens in patients ≥ 70 years (F, $n = 46$; Ch, $n = 41$; FA, $n = 16$; FR, $n = 24$; FRA, $n = 21$), (C) F versus Ch by age, (D) F versus FR by age, (E) F versus FA by age, and (F) FR versus FRA by age. In A-B, median OS estimates are provided in parentheses for each treatment regimen, and the P values were calculated using the log-rank test. The interaction P values in C-F were obtained from a proportional hazards model using Wald tests. Ch, chlorambucil; F, fludarabine; FA, fludarabine with alemtuzumab consolidation; FR, fludarabine with rituximab; FRA, FR with alemtuzumab consolidation.

patients younger than 65 years ($HR = 0.6$, 95% CI, 0.5 to 0.8) and those ≥ 65 years of age ($HR = 0.8$; 95% CI, 0.5 to 1.1). We further explored treating age as a continuous variable and observed that the benefit of fludarabine compared with chlorambucil decreased marginally with age, with estimated hazard ratios of 0.70 (95% CI, 0.56 to 0.89), 0.76 (95% CI, 0.57 to 1.00), and 0.81 (95% CI, 0.57 to 1.16) at

ages 65, 70, and 75 years, respectively. For OS, however, the age versus treatment interaction effect was again statistically significant using the cutoff at 65 years ($P = .03$); OS was improved with fludarabine, decreasing the risk of death by 33% for adults younger than 65 ($HR = 0.67$; 95% CI, 0.5 to 0.9), but was not significantly improved in those age 65 or older ($HR = 1.10$; 95% CI, 0.8 to 1.5; Fig 3B). Modeling age

Fig 3. Kaplan-Meier curves for fludarabine (F) versus chlorambucil (Ch) by age group using cut point of 65 years. (A) Progression-free survival for patients younger than 65 years (F, n = 97; Ch, n = 113) versus patients $\geq$ 65 years (F, n = 80; Ch, n = 73). (B) Overall survival for patients younger than 65 years (F, n = 99; Ch, n = 119) versus patients $\geq$ 65 years (F, n = 80 and Ch, n = 74). The interaction P values were obtained from a proportional hazards model using Wald tests. FR, fludarabine with rituximab.

as a continuous variable showed that the benefit of fludarabine relative to chlorambucil abated at an earlier age for OS than for PFS, with estimated hazard ratios of 0.88 (95% CI, 0.70 to 1.11), 1.01 (95% CI, 0.76 to 1.33), and 1.15 (95% CI, 0.80 to 1.66) at ages 65, 70, and 75 years, respectively.

This difference in PFS for chlorambucil and fludarabine in CALGB 9011 from previous reports could be due to a number of factors. The ORR and PFS with chlorambucil were better in the CLL5 study (ORR, 51%; PFS, 18 months)¹⁰ compared with CALGB 9011 (ORR, 37%; PFS, 14 months), whereas outcomes with fludarabine were similar, perhaps due to differences in chlorambucil dosing between the two studies (40 mg/m² orally every 28 days in CALGB 9011 v 0.4 mg/kg orally every 15 days, increasing as tolerated to 0.8 mg/kg in the CLL5 study). There may be a marginal benefit to fludarabine in this group of patients, especially in fit patients, which is more pronounced with the less effective chlorambucil regimen used in CALGB 9011. There also may be patient-specific differences in the studies, such as more fit patients enrolled on CALGB 9011 in the 65 to 70 years age range who can better tolerate fludarabine. Given the beneficial outcome of rituximab across all age groups and acceptable tolerability of its addition to chlorambucil,^{12,13} this combination could be considered a reasonable choice for this patient population. Currently, the German CLL11 randomized, three-arm study is formally testing chlorambucil versus chlorambucil plus rituximab versus chlorambucil plus GA101, in which a secondary analysis in the subset of older patients could reveal whether this is feasible.

In conclusion, these data show that frontline therapy with fludarabine does not improve outcomes for older adults with CLL as compared with chlorambucil, whereas the addition of rituximab to fludarabine significantly improves PFS and OS in both younger and older patients. As we see more clearly that the optimal therapy for older adults with CLL is not necessarily the same as for younger patients, future studies will need to look specifically at this age group. Given our results as well as the results of the CLL5 study, chlorambucil is a reasonable chemotherapeutic backbone on which to design new combination regimens in this age group. With recent data regarding the combination of chlorambucil and rituximab in older patients,¹²

this combination is certainly a standard therapeutic option for older patients and may be an ideal platform on which to add new targeted agents to improve efficacy. To effectively treat older patients with CLL, new therapies and combinations are needed that are effective yet tolerable even for those patients with comorbid medical conditions or limited performance status.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

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