5-Year Survival in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia in a Randomized, Phase III Trial of Fludarabine Plus Cyclophosphamide With or Without Oblimersen

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ABSTRACT

Purpose

A randomized trial of oblimersen plus fludarabine/cyclophosphamide (OBL-FC; $n = 120$) versus FC ($n = 121$) was conducted in patients with relapsed/refractory chronic lymphocytic leukemia (CLL). The primary end point was met: the complete response (CR) rate, defined as complete or nodular partial response, was significantly greater with OBL-FC than with FC (17% v 7%; $P = .025$). Among patients with CR, response duration was significantly longer with OBL-FC than with FC (median not reached; > 36 months v 22 months; $P = .03$). Maximum benefit with OBL-FC, including a four-fold increase in CR rate and a survival benefit with 3 years of follow-up (hazard ratio, 0.53; $P = .05$), was observed in patients with fludarabine-sensitive disease. We evaluated long-term survival and poststudy CLL therapy among all randomly assigned patients.

Methods

Poststudy CLL treatment information was collected. Patients were observed for survival for up to 5 years from the date of random assignment.

Results

Poststudy CLL treatment was balanced between arms. Intent-to-treat analysis of 5-year survival showed no significant between-treatment difference (hazard ratio, 0.87; $P = .34$). Among the greater than 40% of patients with complete or partial remission, a significant 5-year survival benefit was observed with OBL-FC (hazard ratio, 0.60; $P = .038$). Among patients with fludarabine-sensitive disease who had previously demonstrated maximum benefit with OBL-FC, the previously observed survival benefit improved: a 50% reduction in the risk of death was observed ($P = .004$).

Conclusion

In relapsed/refractory CLL, OBL combined with FC offers patients who achieve complete or partial remission, as well as those who have fludarabine-sensitive disease, a significant survival benefit.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) will be diagnosed in more than 15,000 individuals in 2009 in the United States alone.¹ The disease course is highly variable.²⁻⁴ Some patients have few symptoms and stable disease. Others have "B" symptoms, organomegaly, and lymphadenopathy and may develop anemia, thrombocytopenia, or both, as normal bone marrow cells are progressively replaced by malignant cells.

As initial therapy for CLL, purine nucleoside analog-based therapy (eg, fludarabine, cladribine) remains the most commonly used. On the basis of a large, randomized, CALGB (Cancer and Leukemia

Group B) study, significantly better overall and complete response rates, durations of response, and progression-free survivals were attained with fludarabine as initial therapy compared with the alkylating agent chlorambucil.⁵ Favorable results have been reported in other randomized studies of purine nucleoside analogs administered alone or in combination with other drugs in the front-line setting.⁶⁻⁸ However, these studies have not shown a benefit in overall survival, and the evaluation of a variety of drugs in combination with agents in this class (particularly fludarabine) continues. Three prospective, randomized studies of fludarabine plus cyclophosphamide versus fludarabine as first-line therapy demonstrated significant improvement in multiple

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outcome parameters; however, again, a survival benefit has not yet been realized.⁹⁻¹¹ The monoclonal antibody rituximab frequently is administered in combination with fludarabine and cyclophosphamide, and this combination has promising results, including overall response rates as high as 90% to 95% in previously untreated patients with CLL who received a regimen of fludarabine plus rituximab or of fludarabine, cyclophosphamide, and rituximab.^{12,13}

After a patient has experienced relapse after initial therapy, treatment selection depends largely on disease-related manifestations, prior therapy, and leukemic-cell genomic abnormalities. A variety of pharmacologic agents with different mechanisms of action—purine nucleoside analogs, alkylating agents, and monoclonal antibodies—frequently are employed alone or in combination. On the basis of a large, randomized, multicenter study in patients with relapsed or refractory CLL, fludarabine/cyclophosphamide combined with rituximab prolonged progression-free survival and improved the overall response rate compared with a regimen of fludarabine and cyclophosphamide.¹⁴ Overall, however, few randomized studies have been conducted in the setting of relapsed or refractory disease.

The Bcl-2 protein plays a critical role in CLL.¹⁵⁻¹⁸ Tumorigenicity and tumor aggressiveness depend on Bcl-2 expression in CLL.¹⁹ The antisense oligonucleotide oblimersen (OBL) downregulates Bcl-2 protein.²⁰ Bcl-2 downregulation was correlated with OBL uptake in leukemia cell lines and in acute myeloid leukemia cells from OBL-treated patients.²¹ OBL displayed modest single-agent activity in a phase I/II trial in heavily pretreated patients with relapsed/refractory CLL who had received an average of 3.5 prior treatment regimens.^{22,23} A partial response was achieved in two of the 26 evaluable patients,²² and more than 80% of the patients showed evidence of antileukemic activity, including a reduction in lymphocytosis, organomegaly, or lymphadenopathy (data on file, Genta, Berkeley Heights, NJ).

Preclinically, OBL potentiates the cytotoxic activity of agents commonly used in CLL therapy, including fludarabine,²⁴ alemtuzumab,^{25,26} and rituximab.²⁴ We combined OBL with fludarabine and cyclophosphamide (FC; together, OBL-FC) to determine whether this combination would improve the rate of complete response in patients who had experienced relapse after or who had become refractory to fludarabine-based therapy, and we observed patients for survival for up to 3 years from the date of random assignment.²⁷ As previously reported,²⁷ the primary end point was met: the addition of OBL to FC resulted in a statistically significant increase in the complete response rate. Twenty patients (17%) in the OBL-FC arm achieved a complete response compared with eight patients (7%) in the FC arm ($P = .025$). The overall response rate was not significantly different between treatment arms (41% and 45%, respectively). OBL-FC was superior to FC with respect to complete response rate in each of the three prospectively defined strata. The greatest benefit from the addition of OBL was observed in patients with fludarabine-sensitive disease (ie, those who had a partial response or better for more than 6 months after prior fludarabine therapy and then experienced relapse). Among these patients (OBL-FC arm, $n = 51$; FC arm, $n = 50$), a four-fold increase in the complete response rate was apparent (25% in OBL-FC arm v 6% in the FC arm; $P = .016$). In both arms, all patients with a complete response had a durable response (ie, a response that lasted ≥ 6 months from the date of initial response). Duration of response was significantly longer (> 1 year) with OBL-FC than FC during a minimum of 2 years of follow-up (OBL-FC arm, median not reached but estimated as > 36 months; FC arm median, 22 months;

$P = .03$). Recently we evaluated long-term (ie, 5-year) survival and poststudy CLL therapy among all randomly assigned patients.

METHODS

Patients

As previously described,²⁷ patients who were 18 years of age or older were eligible to participate if they had measurable and active CLL (according to National Cancer Institute Working Group [NCI-WG] Guidelines)²⁸ of intermediate- or high-risk stage (defined on the basis of modified Rai criteria),²⁸ ECOG performance status ≤ 2 , adequate organ function, platelet count $\geq 50,000/\text{mm}^3$ without hematopoietic growth factor or transfusion support, and a negative Coombs' tests (direct and indirect). Additionally, only patients who had received at least one prior chemotherapy regimen with two or more cycles of fludarabine were eligible. Exclusion criteria have been previously reported.²⁷ The trial was conducted in accordance with applicable requirements regarding ethical review and informed consent, including those in the Declaration of Helsinki.

Trial Design and Treatment

Patients were stratified according to three criteria: number of prior regimens (one or two v three or more), duration of response to last therapy (> 6 months $v \leq 6$ months), and prior response to fludarabine (relapsed v refractory). Given this baseline information, a patient was considered to have fludarabine-sensitive disease if disease recurred after a partial response or better had been achieved with fludarabine and had been maintained for more than 6 months. A patient was considered to have fludarabine-refractory disease if a partial response or better had not been achieved or if disease recurred within 6 months of fludarabine treatment; this definition was adapted from the literature.²⁹ Patients were randomly assigned centrally to treatment arms by using a permuted block method.

Treatment was administered every 28 days for up to six cycles. Patients in the control arm received fludarabine 25 $\text{mg}/\text{m}^2/\text{d}$ intravenously over 20 to 30 minutes followed by cyclophosphamide 250 $\text{mg}/\text{m}^2/\text{d}$ intravenously over 30 to 60 minutes on days 1, 2, and 3 of each cycle. Patients in the investigational arm received OBL 3 $\text{mg}/\text{kg}/\text{d}$ on days 1 through 7 by continuous intravenous infusion (via central or peripheral catheter and an ambulatory infusion pump) and the same FC regimen as in the control arm on days 5, 6, and 7. Protocol-specified concomitant medications have been previously reported.²⁷

Response Assessment and Criteria

Response was determined on the basis of all clinical and laboratory data available up to patients' last visits. An independent hematopathologist who was blinded to both treatment assignment and clinical information assessed bone marrow specimens. An expert clinical reviewer who was blinded to study treatment (K.R.R.) determined clinical response and progression according to NCI-WG Guidelines.²⁸ If a computed tomography (CT) scan had been performed at baseline and showed active disease, confirmation of complete response by CT scan was required before bone marrow biopsy. Patients with a complete response were to have bone marrow flow cytometry (restricted to CD5/CD19) within 2 months after the last dose of study drug.

End Points and Statistical Analysis

The primary end point was the relative proportion of patients who achieved a complete response (defined throughout this manuscript as comprising complete or nodular partial response and determined on the basis of the NCI-WG Guidelines).²⁸ Key secondary end points included overall response rate (ie, complete response plus partial response), duration of response, time to progression, and overall survival.

Information on the estimation of sample size has been reported previously.²⁷ Survival was analyzed by using the log-rank test and was presented in Kaplan-Meier curves. By using the Cox proportional hazards model, univariate and multivariate analyses of selected prognostic factors (including the three stratification factors, age, sex, Rai stage, hemoglobin, platelet count, lactate dehydrogenase [LDH], and β_2 microglobulin) for overall survival were performed.

RESULTS

Patient Characteristics and Exposure

Between August 2001 and June 2003, 241 patients were randomly assigned in eight countries (OBL-FC arm, $n = 120$; FC arm, $n = 121$). All but seven patients were observed for up to 5 years from their date of random assignment; these seven patients were lost to follow-up.

The distribution of patients between treatment arms was generally well balanced with respect to baseline characteristics (Table 1).

Table 1. Patient Characteristics at Baseline by Treatment Arm: Intent-to-Treat Population

Characteristic	Treatment Arm			
	OBL-FC ($n = 120$)		FC ($n = 121$)	
	No.	%	No.	%
Sex				
Male	89	74	89	74
Race/ethnicity				
White	105	88	109	90
Black	6	5	7	6
Hispanic	8	7	4	3
Other	1	1	1	1
Age, years				
Median	63		63	
Range	35-86		42-82	
≥ 65	53	44	52	43
≥ 75	17	14	10	8
ECOG performance status				
0	41	34	38	31
≥ 1	78	65	80	66
Unknown	1	1	2	2
Rai stage				
≤ 2	66	55	59	49
3-4	54	45	61	50
Unknown	0	0	1	1
Median time from diagnosis, months	70		58	
No. of prior regimens				
1-2	60	50	63	52
≥ 3	60	50	58	48
Fludarabine sensitivity				
Relapsed	51	43	50	41
Refractory	69	58	71	59
Response to last therapy, months				
> 6	54	45	52	43
≤ 6	66	55	69	57
β_2 microglobulin*				
< 4	57	48	58	48
≥ 4	52	43	47	39
Serum LDH level†				
< ULN range	63	53	63	52
≥ ULN range	53	44	52	43
Platelet count, $\times 10^3/\mu\text{L}$				
< 100,000	43	36	43	36
≥ 100,000	77	64	78	64

Abbreviations: OBL-FC, oblimersen plus fludarabine/cyclophosphamide; FC, fludarabine/cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*Not available for 11 patients in the OBL-FC group and 16 patients in the FC group.

†Not available for four patients in the OBL-FC group and six patients in the FC group.

The percentage of patients 75 years of age or older was greater in the OBL-FC arm than in the FC arm. Median time from diagnosis to random assignment was approximately 12 months longer in the OBL-FC arm than in the FC arm. Longer time from diagnosis was correlated with elevated β_2 microglobulin level, which is a known poor prognostic factor for survival (data not shown).⁴ In both treatment arms, the median number of prior treatment regimens was three, and the median number of prior cycles of fludarabine was six.

A total of 115 patients in each arm received study treatment. The median number of cycles completed in each arm was 4.

Efficacy

Duration of response. During 5 years of follow-up, among the 20 patients with complete response in the OBL-FC arm, 12 patients (60%) were alive; among those 12 patients, five had ongoing complete response, two had experienced relapse but had not initiated new therapy, and five had experienced relapse and initiated new therapy. Among the eight patients with complete response in the FC arm, three patients (38%) were alive, and all three had experienced relapse and initiated new therapy.

Survival. The 5-year survival rate (intent-to-treat analysis) was 25% (ie, 30 of 120 patients) in the OBL-FC arm and 15% (ie, 18 of 121 patients) in the FC arm (Fig 1A; hazard ratio, 0.87; $P = .34$).

The 5-year survival rates among patients with complete or partial response were 47% in the OBL-FC arm and 24% in the FC arm, and this rate was significantly greater with OBL-FC than with FC (hazard ratio, 0.60; $P = .038$; Fig 1B). This reflected an improvement in the survival benefit among responding patients compared with that previously observed with 3-year follow-up (hazard ratio, 0.50; $P = .08$). In the complete response category, more patients were alive at 5 years in the OBL-FC arm (ie, 12 [60%] of 20 patients) than in the FC arm (three [38%] of eight patients). Similarly, an improved 5-year survival rate was observed in the partial response category (11 [38%] of 29 patients in the OBL-FC arm compared with 10 [22%] of 46 patients in the FC arm).

The greatest benefit with OBL was observed in patients with fludarabine-sensitive disease; a 50% reduction in the risk of death ($P = .004$; Fig 1C) reflected improvement in the survival benefit compared with that observed during 3 years of follow-up (hazard ratio, 0.53; $P = .05$). In nonresponding patients, there was no difference between treatment arms in 5-year survival (hazard ratio, 1.0; $P = .91$).

Poststudy CLL treatment data showed no evidence of an imbalance between the two arms either for the intent-to-treat population or among responding patients (Table 2). In fact, for patients with a complete and or partial response, use of poststudy therapy was greater in the FC arm (72%) than in the OBL-FC arm (59%).

Univariate analyses confirmed the prognostic value of the study stratification factors for survival. In addition, baseline β_2 microglobulin (< 4 mg/L $v \geq 4$ mg/L; $P < .0001$) and baseline serum LDH (< upper limit of normal v upper limit of normal or greater; $P < .0001$) were highly prognostic. On the basis of multivariate analyses, the number of prior regimens, age (< 65 years $v \geq 65$ years), baseline β_2 microglobulin (< 4 mg/L $v \geq 4$ mg/L), and baseline serum LDH (< upper limit of normal v upper limit of normal or greater normal) were predictive of survival. Among all prognostic factors examined in multivariate analyses, a significant

Fig 1. Kaplan-Meier survival curves by treatment arm with 5 years of follow-up. (A) Intent-to-treat population (n = 241). (B) Responding patients (ie, patients with a complete or partial response; n = 103). (C) Patients with fludarabine-sensitive disease (n = 101). OBL-FC, oblimersen plus fludarabine/cyclophosphamide; FC, fludarabine/cyclophosphamide.

interaction with treatment was detected only for fludarabine sensitivity; the hazard ratio for treatment effect was 0.48 ($P = .004$). The result is consistent with that from the model unadjusted for these factors (hazard ratio, 0.50; $P = .004$). Safety findings have been reported previously.²⁷

Table 2. Post-Study CLL Therapy by Treatment Arm: Intent-to-Treat Population

Treatment	Treatment Arm (N = 241)			
	OBL-FC (n = 120)		FC (n = 121)	
	No.	%	No.	%
Any post-study therapy	73	61	81	67
Fludarabine or cladribine	28	23	32	26
Cyclophosphamide/chlorambucil	34	28	39	32
Rituximab	32	27	33	27
Alemtuzumab	7	6	11	9
Other	18	15	23	19

Abbreviations: CLL, chronic lymphocytic leukemia; OBL-FC, oblimersen plus fludarabine/cyclophosphamide; FC, fludarabine/cyclophosphamide.

DISCUSSION

There is growing evidence of an association between the quality of response achieved (ie, complete response) and extended survival in patients with CLL.^{30,31} In this randomized study with well balanced treatment arms, a distinct subgroup of patients who achieved complete response had greatly enhanced disease-free survival, which supports earlier findings. OBL was the key difference in this subgroup. Although immunoglobulin heavy chain gene mutational status and cytogenetics were not assessed routinely at the time this trial was initiated, the multiple prior treatments and relapse status of this patient population should have selected for high-risk patients.³²

A complete response was achieved in a significantly greater percentage of patients treated with OBL-FC than with FC alone. Among patients with a complete response in the OBL-FC arm, duration of response was significantly longer. Notably, administration of the OBL-FC combination significantly extended survival in patients who achieved a partial response or better. The achievement of durable complete responses with OBL-FC is advantageous compared with previous therapies. OBL-FC induced response (ie, an increased percentage of complete responses compared with FC alone) and had an attendant survival benefit, as more than 45% of responding patients were alive at 5 years. FC induced response (primarily partial response) and had less than 25% of responding patients alive at 5 years.

Consistent with the proposed mechanism of action of OBL as Bcl-2 downregulation, patients who maximally benefited from the OBL-FC regimen had experienced relapse with fludarabine. The 50% reduction in the risk of death observed among patients with fludarabine-sensitive disease confirms the efficacy of the OBL-FC regimen and warrants evaluation of this regimen in the first-line setting.

Future OBL studies in CLL should include its administration in combination with other standard and novel agents in chemotherapy-naïve patients. The efficacy and safety of an OBL and rituximab combination in non-Hodgkin's lymphoma was demonstrated recently³³; results suggest that this would be a particularly interesting combination in CLL. A study of OBL as a 1-hour intravenous infusion is ongoing in CLL; administration in this manner may be an effective alternative to multiple-day intravenous infusions that have been administered in most prior studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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