

FLUDARABINE COMPARED WITH CHLORAMBUCIL AS PRIMARY THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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ABSTRACT

Background Fludarabine is an effective treatment for chronic lymphocytic leukemia that does not respond to initial treatment with chlorambucil. We compared the efficacy of fludarabine with that of chlorambucil in the primary treatment of chronic lymphocytic leukemia.

Methods Between 1990 and 1994, we randomly assigned 509 previously untreated patients with chronic lymphocytic leukemia to one of the following treatments: fludarabine (25 mg per square meter of body-surface area, administered intravenously daily for 5 days every 28 days), chlorambucil (40 mg per square meter, given orally every 28 days), or fludarabine (20 mg per square meter per day for 5 days every 28 days) plus chlorambucil (20 mg per square meter every 28 days). Patients with an additional response at each monthly evaluation continued to receive the assigned treatment for a maximum of 12 cycles.

Results Assignment of patients to the fludarabine-plus-chlorambucil group was stopped when a planned interim analysis revealed excessive toxicity and a response rate that was not better than the rate with fludarabine alone. Among the other two groups, the response rate was significantly higher for fludarabine alone than for chlorambucil alone. Among 170 patients treated with fludarabine, 20 percent had a complete remission, and 43 percent had a partial remission. The corresponding values for 181 patients treated with chlorambucil were 4 percent and 33 percent ($P < 0.001$ for both comparisons). The median duration of remission and the median progression-free survival in the fludarabine group were 25 months and 20 months, respectively, whereas both values were 14 months in the chlorambucil group ($P < 0.001$ for both comparisons). The median overall survival among patients treated with fludarabine was 66 months, which was not significantly different from the overall survival in the other two groups (56 months with chlorambucil and 55 months with combined treatment). Severe infections and neutropenia were more frequent with fludarabine than with chlorambucil ($P = 0.08$), although, overall, toxic effects were tolerable with the two single-drug regimens.

Conclusions When used as the initial treatment for chronic lymphocytic leukemia, fludarabine yields higher response rates and a longer duration of remission and progression-free survival than chlorambucil; overall survival is not enhanced. (N Engl J Med 2000;343:1750-7.)

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CHLORAMBUCIL has been the standard treatment for chronic lymphocytic leukemia (CLL) for 40 years, but it has not changed the natural history of the disease.¹ Fludarabine, a nucleoside analogue, was found to be effective in patients who had not had a response to chlorambucil, and it also showed promise in uncontrolled trials as initial therapy for CLL.²⁻⁸

In 1990, we began a prospective comparison of fludarabine with chlorambucil in previously untreated patients with CLL. While this study was in progress, the results of two other randomized trials were published.⁹⁻¹¹ Both studies found that fludarabine was superior to chlorambucil in patients with previously untreated CLL. We present here the results of our study of the efficacy of fludarabine and chlorambucil in such patients.

METHODS

Criteria for Eligibility

The diagnosis of CLL was based on criteria recommended in 1988 by the working group on CLL sponsored by the National Cancer Institute (NCI).¹² The stage of disease was assessed according to the guidelines of the NCI working group¹² and the modified Rai staging system.^{13,14} All patients in the high-risk category (Rai stage III or IV) were eligible. Intermediate-risk patients (Rai stage I or II) were also eligible if they had at least one of the following: any disease-related symptom such as weight loss, extreme fatigue, night sweats, or fever without evidence of infection; massive or progressive splenomegaly or lymphadenopathy, or both; or more than a 50 percent increase in the number of peripheral-blood lymphocytes over a 2-month period or an anticipated doubling of these cells within less than 12 months. Patients who had previously received any cytotoxic therapy were not eligible. Additional eligibility requirements were an age of at least 18 years; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; base-line values for liver and kidney function that were no greater than 1.5 times the upper limits of normal; and a negative direct antiglobulin (Coombs') test. Each patient signed an informed-consent form approved by a local institutional review board. Submission of blood smears, bone marrow aspirates, and biopsy slides for central pathological review was required. Central review was also required for specimens from patients who had a complete remission.

Randomized Treatment and Crossover

The Cancer and Leukemia Group B statistical center was responsible for the random assignment of patients to one of the fol-

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lowing treatments: fludarabine (25 mg per square meter of body-surface area, administered intravenously over a period of 10 to 30 minutes on days 1 through 5 every 28 days), chlorambucil (40 mg per square meter given orally once every 28 days), or fludarabine (20 mg per square meter given intravenously on days 1 through 5 every 28 days) plus chlorambucil (20 mg per square meter given orally once every 28 days). The treatments were repeated monthly (every 28 days) for a maximum of 12 cycles. They were stopped sooner in patients who had disease progression, a complete remission, or a response that plateaued over two months of treatment. Patients received oral allopurinol (300 mg per day for 9 days) from the day before chemotherapy began through day 8 during each 28-day treatment cycle for the first three cycles, and thereafter according to the judgment of their physicians.

All patients were evaluated monthly, before the next scheduled cycle of treatment, to assess the toxic effects of the drugs and clinical response. Patients in the fludarabine group or the chlorambucil group who did not have a partial remission or who had evidence of disease progression were allowed to cross over to the other drug. In addition, patients who relapsed within six months after stopping fludarabine or chlorambucil therapy were started on treatment with the other drug. Patients who relapsed more than six months after stopping therapy were treated again with the original drug. All patients assigned to the fludarabine-plus-chlorambucil group who did not have a response or who relapsed within six months after stopping therapy were removed from the study and treated at the discretion of their physicians.

Criteria for a Response

We used the criteria recommended by the NCI-sponsored working group on CLL¹² to evaluate responses. A complete remission was defined as the absence of constitutional symptoms and of lymphadenopathy, splenomegaly, and hepatomegaly on physical examination; an absolute neutrophil count of at least 1500 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a hemoglobin level higher than 11 g per deciliter (without transfusion), and an absolute lymphocyte count of less than 4000 per cubic millimeter; and bone marrow of normal cellularity, with less than 30 percent lymphocytes and no lymphoid nodules. (Bone marrow biopsy was required two months after clinical evidence of a complete remission was present.) A partial remission was defined as a reduction of at least 50 percent in the size of the lymph nodes, spleen, and liver on physical examination, if they were enlarged before therapy; a decrease of at least 50 percent in the number of peripheral-blood lymphocytes from the value before treatment; an absolute neutrophil count of at least 1500 per cubic millimeter or an increase of at least 50 percent over the base-line value; a platelet count of at least 100,000 per cubic millimeter or an increase of at least 50 percent over the base-line value; and a hemoglobin level of at least 11 g per deciliter or an increase of at least 50 percent over the base-line value (without transfusion).

Progressive disease was defined as an increase of at least 50 percent in the size of the lymph nodes, spleen, or liver if they were previously enlarged, or the detection of enlargement if they were not previously enlarged; an increase of at least 50 percent in the number of peripheral-blood lymphocytes; or both. Patients who did not meet any of these criteria were considered to have stable disease.

Modifications of Doses

Guidelines for reductions in the doses of fludarabine and chlorambucil were based on toxic effects that were assessed with the use of the Cancer and Leukemia Group B Expanded Common Toxicity Criteria. The doses of fludarabine and chlorambucil were reduced by 50 percent in patients who had grade 2 pulmonary, renal, hepatic, or other toxic effects. In those with toxic effects graded 3 or higher, treatment was suspended, and decisions about resumption at a decreased dose were made on a case-by-case basis. Treatment was suspended during the course of any major infection; after recovery, the doses of drugs were set 50 percent lower than the original dose.

Statistical Analysis

This study began in October 1990 and was closed to enrollment in December 1994, when 544 patients had been enrolled. We originally aimed for a sample of 450 patients, which we calculated would provide adequate statistical power for the detection of a difference in the rates of complete remission between the chlorambucil group and either of the two groups assigned to receive fludarabine.¹⁵ A planned interim analysis in 1993, in which truncated O'Brien–Fleming boundaries¹⁵ were used, showed that the response rate in the chlorambucil group was significantly lower than the rates in the other two groups. The protocol was then modified to make progression-free survival the main end point; the target sample size remained the same.

In May 1994, when 450 patients had been enrolled in the trial, the fludarabine-plus-chlorambucil group was closed because a second planned interim analysis found excessive rates of life-threatening toxic effects with the combined treatment. Further care of patients in this group was at the discretion of their physicians, and the patients were followed only to assess survival and the occurrence of a second cancer. Also in May 1994 (after the interim analysis), we found that the overall median progression-free survival in the fludarabine group and the chlorambucil group was longer than we had anticipated; for purposes of statistical power, we decided to enroll an additional 94 patients (revised target sample, 544 patients).

All patients who underwent randomization were included in the analysis. The chi-square test was used to compare the response rates in the study groups. All time-to-event distributions were calculated by the Kaplan–Meier method¹⁶ and compared with the use of the log-rank test, with one or two degrees of freedom.¹⁷ The duration of response was measured from the time an initial response was documented to the time of disease progression or death. Progression-free survival was measured from the time of randomization to the time of disease progression or death. Patients who withdrew after starting therapy, who were withdrawn because of drug toxicity or a complicating disease, or who crossed over to the other treatment for reasons other than those defined in the study protocol were followed for progression-free survival. Overall survival was measured from the time of randomization to the time of death from any cause, without adjustment for crossover. All statistical tests were two-sided.

RESULTS

The analysis reported here is based on data collected through June 1999. We assigned 195 patients to receive fludarabine, 200 to receive chlorambucil, and 149 to receive fludarabine plus chlorambucil. Thirty-two patients (15, 7, and 10, respectively, in the three groups) were considered ineligible, and 3 patients (1 in the fludarabine group and 2 in the fludarabine-plus-chlorambucil group) dropped out before beginning treatment, leaving 509 patients (179, 193, and 137, respectively) who form the basis of our report.

Table 1 provides the demographic and clinical characteristics of these patients. There were no imbalances among the three groups with respect to clinical features and risk categories. Survival data were available for 507 of the 509 patients; 474 could be evaluated for a therapeutic response; 477 could be evaluated for drug toxicity; and 172 patients in the fludarabine group and 183 patients in the chlorambucil group could be evaluated for progression-free survival.

Clinical Response

As Table 2 shows, the rates of complete remission and of complete remission plus partial remission were

TABLE 1. PRETREATMENT CHARACTERISTICS OF THE ELIGIBLE PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.

CHARACTERISTIC	FLUDARABINE (N=179)	CHLORAMBUCIL (N=193)	FLUDARABINE PLUS CHLORAMBUCIL (N=137)
Sex (%)			
Male	71	67	66
Female	29	33	34
Age group (%)			
≤39 yr	1	3	2
40–49 yr	13	13	13
50–59 yr	22	24	27
60–69 yr	34	38	35
≥70 yr	30	22	23
Age (yr)			
Median	64	62	63
Range	33–88	36–89	32–83
Race or ethnic group (%)			
White	88	87	91
Black	10	12	8
Hispanic	1	<1	<1
Asian or other	1	<1	<1
Rai stage (%)			
I or II (intermediate risk)	61	59	61
III or IV (high risk)	39	41	39
ECOG performance status (%)*			
0	63	63	52
1	32	33	41
2	5	4	6
White-cell count (per mm ³)			
Median	81,900	80,900	78,900
Range	9000–709,000	8000–588,000	5000–697,000
Platelet count (per mm ³)			
Median	155,000	147,000	143,000
Range	12,000–451,000	10,000–431,000	27,000–409,000
Hemoglobin (g/dl)			
Median	12.2	12.2	11.9
Range	4.6–16.6	5.3–16.7	6.3–16.3

*ECOG denotes Eastern Cooperative Oncology Group.

TABLE 2. CLINICAL RESPONSES ACCORDING TO TREATMENT ASSIGNMENT.*

VARIABLE	FLUDARABINE (N=170)	CHLORAMBUCIL (N=181)	FLUDARABINE PLUS CHLORAMBUCIL (N=123)
	number (percent)		
Complete remission	34 (20)	8 (4)	24 (20)
Partial remission	73 (43)	59 (33)	51 (41)
Complete or partial remission	107 (63)	67 (37)	75 (61)
Stable or progressive disease	63 (37)	114 (63)	48 (39)

*The P values were less than 0.001 for the comparisons of fludarabine with chlorambucil and of fludarabine plus chlorambucil with chlorambucil alone, in terms of both the rate of complete remission and the overall response rate.

significantly higher in both groups treated with fludarabine than in the chlorambucil group ($P<0.001$ for both comparisons). There was no significant advantage to combination treatment over fludarabine alone in terms of the response rates.

The median duration of response was significantly longer ($P<0.001$) among the 107 patients who had either a complete or a partial remission with fludarabine alone (25 months) than among the 67 patients with a response who were treated with chlorambucil alone (14 months) (Fig. 1). There was a significantly longer median time to the progression of disease among the patients treated with fludarabine (20 months) than among those treated with chlorambucil (14 months, $P<0.001$) (Fig. 2).

Overall Survival

There were no significant differences in overall survival among the three groups ($P=0.21$) or between the fludarabine group and the chlorambucil group ($P=0.10$) (Fig. 3). The median duration of follow-up was 62 months. The results for the fludarabine

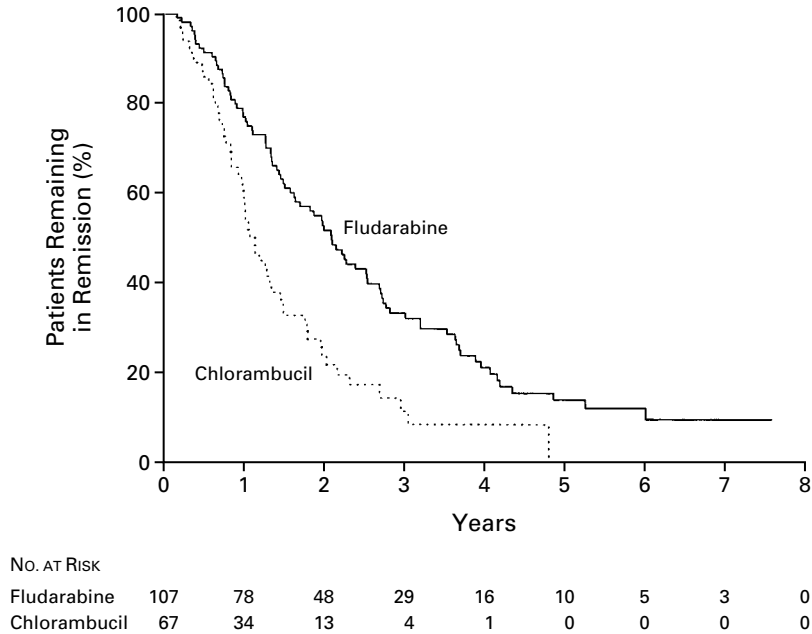


Figure 1. Proportion of Patients with an Initial Response to Fludarabine or Chlorambucil Who Continued in Remission.

Shown are the proportions of the 107 patients assigned to fludarabine and the 67 assigned to chlorambucil who had a response to treatment and remained in complete or partial remission. In both groups combined, 78 percent of patients (135 of 174) had relapses. The median duration of the response was significantly longer in the fludarabine group than in the chlorambucil group (25 vs. 14 months, $P < 0.001$).

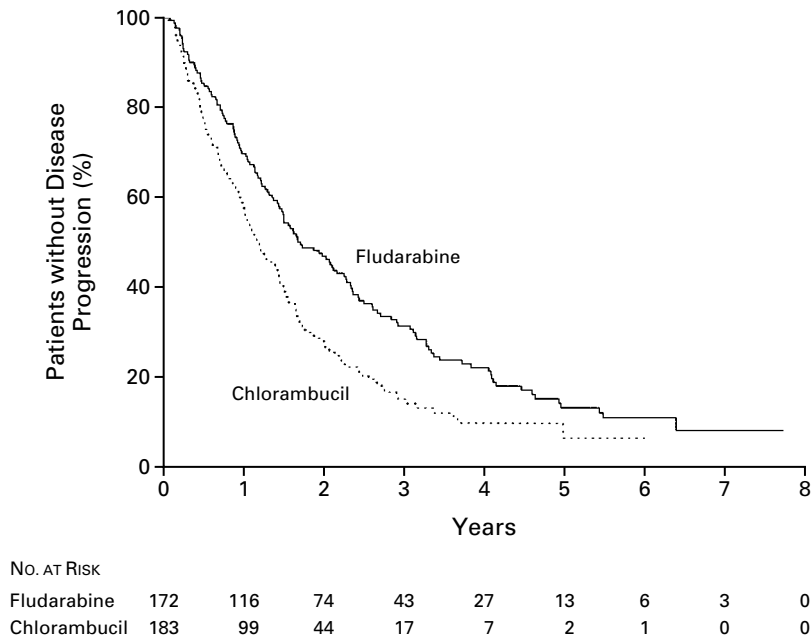


Figure 2. Proportion of Patients without Disease Progression, According to Treatment Group.

Shown are the proportions of the 172 patients assigned to fludarabine and the 183 assigned to chlorambucil in whom disease progression could be evaluated who did not have progression of disease from the time of entry into the study. The disease progressed in 79 percent and 81 percent of the patients in the two groups, respectively. The median time to progression was significantly longer in the fludarabine group than in the chlorambucil group (20 vs. 14 months, $P < 0.001$).

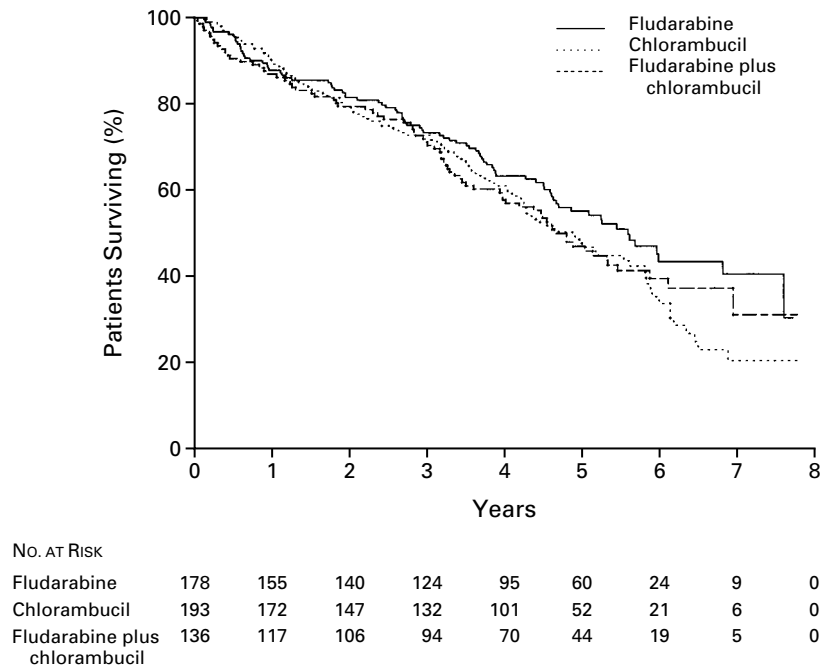


Figure 3. Overall Survival According to Treatment Group.

Shown are the proportions of 178 patients assigned to fludarabine, 193 assigned to chlorambucil, and 136 assigned to fludarabine plus chlorambucil who were still alive during follow-up. Forty-seven percent, 57 percent, and 56 percent of the patients in the three groups, respectively, died. There was no statistically significant difference in overall survival among the three groups (median, 66 months, 56 months, and 55 months, respectively; $P=0.21$).

group and the chlorambucil group include data for patients who crossed over and for those who were treated again with the originally assigned drug; the results thus represent a comparison of the initial treatments. The median survival times for the groups that received fludarabine, chlorambucil, and fludarabine plus chlorambucil were 66, 56, and 55 months, respectively.

Response According to Rai Stage

Treatment with fludarabine resulted in significantly higher rates of complete remission and of complete or partial remission than did treatment with chlorambucil among the intermediate-risk patients (complete remission, $P<0.001$; complete or partial remission, $P=0.002$) and among the high-risk patients (complete remission, $P=0.03$; complete or partial remission, $P<0.001$) (Table 3). Fludarabine was superior to chlorambucil in prolonging the time to disease progression both among the intermediate-risk patients (median, 23 vs. 16 months; $P=0.02$) and among the high-risk patients (median, 18 vs. 12 months; $P=0.006$).

Crossover

Of the 79 patients who crossed over from chlorambucil to fludarabine, 46 percent had a complete

or partial remission. However, of the 29 patients who crossed over from fludarabine to chlorambucil, only 7 percent had a response ($P<0.001$).

Side Effects

All side effects were graded on a six-point scale, with 0 defined as none, 1 as mild, 2 as moderate, 3 as severe, 4 as life-threatening, and 5 as lethal. Most side effects in the three groups were of grade 1 or 2. Only one treatment-related death was recorded, in a patient who had pulmonary and cardiac complications after fludarabine treatment. Among all other side effects, grade 3 or 4 thrombocytopenia, neutropenia, and infections were noteworthy (Table 4). Table 4 also lists the overall incidence of grade 3 and grade 4 side effects of all types in each of the three treatment groups.

DISCUSSION

Our findings demonstrate that in the initial treatment of CLL, fludarabine is superior to chlorambucil. The rate of complete remission and the overall rate of response (complete or partial remission), as well as the duration of the response and of progression-free survival, were significantly better among patients treated with fludarabine than among those given chlorambucil. Treatment with fludarabine plus chloram-

TABLE 3. CLINICAL RESPONSES ACCORDING TO RAI STAGE AND TREATMENT ASSIGNMENT.

TYPE OF RESPONSE	STAGE I OR II (INTERMEDIATE RISK)			STAGE III OR IV (HIGH RISK)		
	FLUDARABINE (N=103)	CHLORAMBUCIL (N=111)	FLUDARABINE PLUS CHLORAMBUCIL (N=77)	FLUDARABINE (N=67)	CHLORAMBUCIL (N=70)	FLUDARABINE PLUS CHLORAMBUCIL (N=46)
	percent					
Complete remission	26	6	22	10	1	15
Partial remission	41	40	42	46	21	41
Complete or partial remission	67	46	64	57	23	56

TABLE 4. PROPORTION OF PATIENTS WITH SEVERE (GRADE 3) OR LIFE-THREATENING (GRADE 4) SIDE EFFECTS.*

SIDE EFFECT	FLUDARABINE (N=170)	CHLORAMBUCIL (N=178)	FLUDARABINE PLUS CHLORAMBUCIL (N=129)	P VALUE	
				FLUDARABINE VS. CHLORAMBUCIL	FLUDARABINE PLUS CHLORAMBUCIL VS. CHLORAMBUCIL
	percent				
Thrombocytopenia	13	14	43	0.81	<0.001
Neutropenia	27	19	43	0.08	0.007
Infection	16	9	28	0.08	0.01
Grade 3 or 4 side effect of any type	55	44	81	0.05	<0.001

*Each side effect was recorded at least once.

bucil produced response rates similar to those with fludarabine alone, but with greater toxicity.

Our results are concordant with the findings of two large, randomized studies⁹⁻¹¹ conducted at approximately the same time as our study. These studies are known as the European study⁹ and the French study.^{10,11} The control group in the European study received cyclophosphamide, doxorubicin, and prednisone (CAP), and in the French study there were two control groups: one received CAP, and the other received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The rate of complete remission in the French study was higher than the rates in other studies, perhaps because the definition of complete remission in the French study differed from that of the NCI working group and because it did not require an examination of the bone marrow. North American physicians rarely use CAP for the treatment of CLL and almost never use CAP or CHOP for initial treatment.

When we analyzed responses according to the stage

of disease, fludarabine was significantly superior to chlorambucil among both the intermediate-risk patients (with stage I or II disease) and the high-risk patients (stage III or IV). We cannot, however, conclude from these results that it is preferable to start fludarabine therapy in patients with intermediate-risk CLL.

Although the toxicity of fludarabine plus chlorambucil forced its discontinuation before the completion of enrollment in our study, the two single-drug regimens were well tolerated, with an acceptable level of toxicity. However, the incidence of grade 3 and grade 4 neutropenia and infections was greater with fludarabine than with chlorambucil, and the combined incidence of all grade 3 and grade 4 side effects was significantly greater with fludarabine than with chlorambucil. The toxicity of fludarabine in the French study^{10,11} was similar to that which we observed.

The incidence of severe infections reported here took into account infections that we considered to be a consequence of the treatment. A subsequent

retrospective analysis showed a significantly higher incidence of major infections (those requiring hospitalization or treatment with parenteral antibiotics), whether they were related to the disease or to treatment, among patients who received fludarabine (incidence of major infections, 29 percent, 17 percent, and 45 percent in the fludarabine, chlorambucil, and fludarabine-plus-chlorambucil groups, respectively).¹⁸

It is likely that the results of treatment of CLL will be improved through small, incremental steps that increase the rates of remission. We have come to the end of a long period — 40 years — in which therapy was limited mainly to chlorambucil. These four decades were marked by a lack of progress and persistently low rates of objectively measured responses. Now, a significant increase in the rate of remission has been demonstrated with fludarabine. The challenge before us is to find other effective agents that, when combined with fludarabine, will lead to more incremental advances and, ultimately, to increased survival among patients with CLL.

Although intravenous fludarabine therapy is less convenient than oral chlorambucil, it offers the possibility of a prolonged progression-free interval during which no therapy is required. In older patients with other medical problems, the ease of administration of oral chlorambucil has obvious advantages. Patients and their physicians therefore still confront a decision about which drug to try first in the case of previously untreated, progressive CLL. The information from this trial provides a framework for making such decisions.

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APPENDIX

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REFERENCES

1. Dighiero G, Maloum K, Desablens B, et al. Chlorambucil in indolent chronic lymphocytic leukemia. *N Engl J Med* 1998;338:1506-14.
2. Grever MR, Kopecky KJ, Coltman CA, et al. Fludarabine monophosphate: a potentially useful agent in chronic lymphocytic leukemia. *Nouv Rev Fr Hematol* 1988;30:457-9.
3. Keating MJ, Kantarjian H, Talpaz M, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. *Blood* 1989;74:19-25.
4. Keating MJ, Kantarjian H, O'Brien S, et al. Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. *J Clin Oncol* 1991;9:44-9.
5. Robertson LE, Huh YO, Butler JJ, et al. Response assessment in chronic lymphocytic leukemia after fludarabine plus prednisone: clinical, pathologic, immunophenotypic, and molecular analysis. *Blood* 1992;80:29-36.
6. Keating MJ, O'Brien S, Kantarjian H, et al. Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. *Blood* 1993;81:2878-84.
7. O'Brien S, Kantarjian H, Beran M, et al. Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment. *Blood* 1993;82:1695-700.
8. Keating MJ, O'Brien S, Lerner S, et al. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. *Blood* 1998;92:1165-71.
9. French Cooperative Group on CLL, Johnson S, Smith AG, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukemia. *Lancet* 1996;347:1432-8.
10. Lepage M, Chevret S, Cazin B, et al. Randomized clinical trial comparing two anthracyclin-containing regimens (CHOP and CAP) and fludarabine (FDR) in advanced chronic lymphocytic leukemia (CLL). *Blood* 1999;94:Suppl 1:603a. abstract.
11. The French Cooperative Group on Chronic Lymphocytic Leukemia. Comparison of fludarabine, cyclophosphamide/doxorubicin/prednisone, and cyclophosphamide/doxorubicin/vincristine/prednisone in advanced forms of chronic lymphocytic leukemia: preliminary results of a controlled clinical trial. *Semin Oncol* 1993;20:Suppl 7:21-3.
12. Cheson BD, Bennett JM, Rai KR, et al. Guidelines for clinical protocols for chronic lymphocytic leukemia: recommendations of the National Cancer Institute-sponsored working group. *Am J Hematol* 1988;29:152-63.
13. Rai KR. A critical analysis of staging in CLL. In: Gale RP, Rai KR, eds. *Chronic lymphocytic leukemia: recent progress and future directions*. New York: Alan R. Liss, 1987:253-64.
14. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34.
15. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;54:457-81.
17. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
18. Morrison VA, Rai KR, Peterson B, et al. The impact of therapy with chlorambucil (C), fludarabine (F) or fludarabine + chlorambucil (F + C) on infections in patients with chronic lymphocytic leukemia (CLL): an intergroup study (CALGB9011). *Blood* 1998;92:Suppl 1:490a. abstract.

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