

CHLORAMBUCIL IN INDOLENT CHRONIC LYMPHOCYTIC LEUKEMIA

GUILLAUME DIGHIÉRO, M.D., PH.D., KARIM MALOUM, M.D., PH.D., BERNARD DESABLENS, M.D., BRUNO CAZIN, M.D., MAURICE NAVARRO, M.D., ROBERT LEBLAY, M.D., MICHEL LEPORRIER, M.D., JÉROME JAUBERT, M.D., GÉRARD LEPEU, M.D., BRIGITTE DREYFUS, M.D., JACQUES-LOUIS BINET, M.D., AND PHILIPPE TRAVADE, M.D., FOR THE FRENCH COOPERATIVE GROUP ON CHRONIC LYMPHOCYTIC LEUKEMIA

ABSTRACT

Background To determine whether chlorambucil treatment benefits patients with indolent chronic lymphocytic leukemia (CLL), we conducted two randomized trials in 1535 patients with previously untreated stage A CLL.

Methods In the first trial, 609 patients were randomly assigned to receive either daily chlorambucil or no treatment; in the second trial, 926 patients were randomly assigned to receive either intermittent chlorambucil plus prednisone or no treatment. Median follow-up for the first and second trials exceeded 11 and 6 years, respectively. The end points were overall survival, response to treatment, and disease progression.

Results Treatment of indolent CLL did not increase survival in either trial. In the treated group, as compared with the untreated group, the relative risk of death was 1.14 (95 percent confidence interval, 0.92 to 1.41; $P=0.23$) in the first trial and 0.96 (95 percent confidence interval, 0.75 to 1.23; $P=0.74$) in the second trial, with 76 percent and 69 percent of patients, respectively, having a response to therapy. Although chlorambucil slowed disease progression, there was no effect on overall survival. In the untreated group in the first trial, 49 percent of patients did not have progression to more advanced disease and did not need therapy after follow-up of more than 11 years; however, 27 percent of patients with stage A CLL died of causes related to the disease.

Conclusions Chlorambucil does not prolong survival in patients with stage A CLL. Since deferring therapy until the disease progresses to stage B or C does not compromise survival, treatment of indolent CLL is unnecessary. (N Engl J Med 1998;338:1506-14.)

©1998, Massachusetts Medical Society.

MANY patients with chronic lymphocytic leukemia (CLL) have long lives and die of causes unrelated to the disease.^{1,2} Rai's classification³⁻⁵ and Binet's staging system⁶ have improved the identification of the indolent form of the disease (Table 1), and both ways of staging CLL accurately identify patients with a good prognosis. Of all patients with CLL, 31 percent have Rai stage 0, whereas 63 percent have Binet stage A. Among patients with Rai stage 0, 59 percent are alive 10 years after the diagnosis, and among those with Binet's stage A the 10-year survival rate is 51 percent.¹

There is no evidence that treatment of CLL with chlorambucil affects survival, but this alkylating agent can relieve symptoms in many patients.⁷⁻¹⁴ It is not clear whether therapy benefits patients with the indolent form of CLL. An early report from our group failed to show differences in survival between patients who were treated with chlorambucil immediately after the diagnosis of stage A CLL and those who were not treated.¹⁴ We now report the long-term results of the first trial and a second trial in which 926 previously untreated patients with stage A CLL were randomly assigned to either no treatment or a combination of chlorambucil and prednisone.

METHODS

Patients and Treatments

Both trials included only previously untreated patients with stage A CLL. Patients with prolymphocytic leukemia, a second neoplasm other than basal-cell carcinoma, a positive Coombs' test, or in the second trial, contraindications to prednisone were excluded.

Thirty-one centers participated in the first trial and 46 in the second trial, and randomization was performed by telephone at a centralized location. The first trial enrolled 609 patients between 1980 and 1985 and randomly assigned 308 patients to no treatment and 301 patients to 0.1 mg of chlorambucil per kilogram of body weight per day. The second trial enrolled 926 patients between 1985 and 1990 and randomly assigned 466 patients to no treatment and 460 patients to 0.3 mg of chlorambucil per kilogram per day for five days every month and 40 mg of prednisone per square meter of body-surface area per day for five days every

From the Unité d'Immuno-Hématologie et d'Immunopathologie, Institut Pasteur, Paris (G.D.); Département d'Hématologie, Hôpital Pitié-Salpêtrière, Paris (K.M., J.-L.B.); Service des Maladies du Sang, Centre Hospitalier Régional-Hôpital Sud, Amiens (B. Desablens); Service des Maladies du Sang, Hôpital Claude Huriez, Lille (B.C.); Service des Maladies du Sang, Centre Hospitalier Universitaire-Hôpital Lapeyronie, Montpellier (M.N.); Service de Médecine G, Centre Hospitalier Régional-Hôpital Sud, Rennes (R.L.); Service Hématologie Clinique, Centre Hospitalier Universitaire de Caen, Caen (M.L.); Département d'Hématologie, Centre Hospitalier Universitaire-Hôpital Nord, Saint-Etienne (J.J.); Onco-Hématologie, Maladies Infectieuses, Centre Hospitalier Avignon-Hôpital Henri Duffaut, Avignon (G.L.); Département d'Hématologie et d'Oncologie Virale, Centre Hospitalier Universitaire-Hôpital Jean Bernard, Poitiers (B. Dreyfus); and Unité d'Hématologie Clinique, Hôtel-Dieu, Clermont-Ferrand (P.T.) — all in France. Address reprint requests to Dr. Dighiero at Unité d'Immuno-Hématologie et d'Immunopathologie, Institut Pasteur, 28 rue du Dr. Roux, F-75724 Paris CEDEX 15, France.

Other authors were François-Louis Turpin, M.D. (Oncologie Médicale et Hématologie, Centre René Huguenin, St. Cloud, France), Gérard Terrian, M.D. (Laboratoire d'Hématologie, d'Immunologie, et de Cytogénétique, Hôpital Bicêtre, Le Kremlin Bicêtre, France), and Agnès Bichoffe, M.D. (Département de Médecine Interne, Centre Hospitalier Général de Montluçon, Montluçon, France).

TABLE 1. STAGING SYSTEMS USED FOR CHRONIC LYMPHOCYTIC LEUKEMIA.*

SYSTEM AND RISK	STAGE	DEFINITION	PERCENTAGE OF PATIENTS WITH CLL IN STAGE	SURVIVAL	
				MEDIAN yr	10-YEAR %
Rai staging system					
Low	0	Lymphocytosis only	31	>10	59
Intermediate	I	Lymphocytosis and lymphadenopathy	35	9	
	II	Lymphocytosis and splenomegaly with or without lymphadenopathy or hepatomegaly	26	5	
High	III	Lymphocytosis and anemia, with or without organomegaly	6	2	
	IV	Lymphocytosis, anemia, and thrombocytopenia, with or without organomegaly	2	2	
Binet staging system					
Low	A	Lymphocytosis, with enlargement of <3 lymphoid areas†	63	>10	51
	A'	Stage A with lymphocyte count of $\leq 30,000/\text{mm}^3$ and hemoglobin concentration of ≥ 120 g/liter	49	>10	56
	A''	Stage A with lymphocyte count of $> 30,000/\text{mm}^3$, hemoglobin concentration of < 120 g/liter, or both	14	7	38
Intermediate	B	Lymphocytosis, with enlargement of ≥ 3 lymphoid areas	30	5	
High	C	Lymphocytosis and either anemia or thrombocytopenia, or both	7	2	

*Data were obtained from Rai et al.,³ Binet et al.,⁶ and the French Cooperative Group on Chronic Lymphocytic Leukemia.⁷

†The following lymphoid areas are included: cervical, axillary, and inguinal (whether unilateral or bilateral), spleen, and liver.

month. In the first trial, chlorambucil was administered until clinical resistance to the drug was observed. In the second trial, the planned duration of treatment was three years.

In the first trial, patients whose disease progressed from stage A to stage B were treated with daily chlorambucil if they were previously untreated, or with a combination of cyclophosphamide, vincristine, and prednisone (COP) if they were in the chlorambucil group. Patients enrolled in the second trial whose disease progressed to stage B were given intermittent chlorambucil plus prednisone if they were previously untreated or a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) if they were in the group treated with chlorambucil plus prednisone. Progression to stage C warranted COP for previously untreated patients in the first trial, CHOP for treated patients in the first trial and untreated patients in the second trial, or CHOP plus methotrexate for patients in the treated group in the second trial.

End Points

The primary end points were overall survival, mortality related to CLL, response to treatment, and disease progression. A clinical and hematologic response was defined as the absence of lymphadenopathy, a lymphocyte count of less than 4000 per cubic millimeter, a hemoglobin concentration of more than 100 g per liter, and a platelet count of more than 100,000 per cubic millimeter. Bone marrow biopsy or aspiration was recommended but not required for patients who had clinical and hematologic responses. A partial response was defined as a reduction of at least 75 percent in the initial lymphocyte count and at least 50 percent in each of the initially enlarged lymph nodes. Resistance to treatment or treatment failure was defined as the occurrence of any or all of the following: progression of disease to stage B or C, the lack of a reduction of at least 50 percent in the enlarged lymph nodes, or the lack of a reduction of at least 75 percent in the absolute lymphocyte count.

Causes of death were divided into those related to CLL and those unrelated to CLL; the latter category included only deaths that were unambiguously unrelated to CLL. Deaths related to second neoplasms were recorded separately and considered to be related to CLL. Since an increased number of such deaths was seen in the chlorambucil-treated group in the initial analysis of the first trial, the incidence of cancer was examined in the two trials. To evaluate the response, a follow-up examination was scheduled during the ninth month in the first trial and the sixth month in the second trial. Thereafter, a follow-up examination was scheduled every six months.

Statistical Analysis

Statistical analysis was carried out on an intention-to-treat basis. This analysis was based on findings on the reference date of the scheduled fifth interim analysis for the first trial (July 1, 1994) and the third interim analysis for the second trial (January 1, 1994). Survival analysis was based on Kaplan–Meier estimates,¹⁵ the log-rank test,¹⁶ and the Cox regression model.¹⁷ All P values are two-sided and adjusted for repeated analyses. To account for the five planned interim analyses, a threshold alpha level of 0.0158 was used in order to guarantee an overall type I error of 0.05.¹⁸

RESULTS

Characteristics of the Patients

The median follow-up of survivors was 129 months (range, 6 to 169) in the first trial and 73 months (range, 6 to 106) in the second trial. Three patients in the first trial and six patients in the second were excluded from the analysis because of the lack of information after randomization. There were slightly higher blood lymphocyte counts and degrees

TABLE 2. CHARACTERISTICS OF THE PATIENTS AT RANDOMIZATION.*

CHARACTERISTIC	FIRST TRIAL		SECOND TRIAL	
	NO TREATMENT (N=308)	DAILY CHLORAMBUCIL (N=301)	NO TREATMENT (N=466)	CHLORAMBUCIL PLUS PREDNISONE (N=460)
Age — yr	66±9	65±9	64±9	64±9
Male sex — no. (%)	187 (61)	179 (59)	283 (61)	278 (60)
Lymphoid area involved — no. (%)				
Cervical	75 (24)	65 (22)	108 (23)	98 (21)
Axillary	96 (31)	64 (21)	96 (21)	100 (22)
Inguinal	27 (9)	22 (7)	20 (4)	28 (6)
Splenomegaly — no. (%)	40 (13)	31 (10)	51 (11)	49 (11)
Hepatomegaly — no. (%)	12 (4)	8 (3)	7 (2)	8 (2)
Degree of bone marrow infiltration — %	55±20	57±19	56±20	55±19
Lymphocyte count — ×10 ⁻³ /mm ³	20±17	24±20	26±27	24±21
Hemoglobin — g/liter	141±14	143±14	141±14	141±14
Platelet count — ×10 ⁻³ /mm ³	226±74	231±80	238±70	238±74
Binet stage — no. (%)				
A'	246 (80)	226 (75)	327 (70)	325 (71)
A''	62 (20)	75 (25)	139 (30)	135 (29)

*Plus-minus values are means ±SD.

of bone marrow infiltration in the daily-chlorambucil group in the first trial. There were no significant differences between the groups in either trial at the time of randomization (Table 2).

Survival

The First Trial

In the first trial, 344 deaths were reported (Fig. 1), 169 in the untreated group (5-year survival, 80 percent; 10-year survival, 54 percent) and 175 in the treated group (5-year survival, 76 percent; 10-year survival, 47 percent) (relative risk of death, 1.14 in the treated group as compared with the untreated group; 95 percent confidence interval, 0.92 to 1.41; $P=0.23$ by the log-rank test). In the untreated group, 54 of the 169 deaths were unrelated to CLL, 22 were caused by a second neoplasm, and no cause was found in 9. Death was considered to be related to CLL in 84 patients (due to disease progression in 41, infection in 36, iatrogenic causes in 2, thrombocytopenia in 1, and other causes in 4). In the treated group, 47 of the 175 deaths were unrelated to CLL, 28 were the consequence of a second cancer, and no cause was found in 6. Death was related to CLL in 94 patients (due to disease progression in 45, infection in 41, iatrogenic complications in 6, and autoimmune hemolytic anemia in 2). The distribution of deaths related to CLL was similar in the two groups ($P=0.11$ by the log-rank test) (Fig. 2).

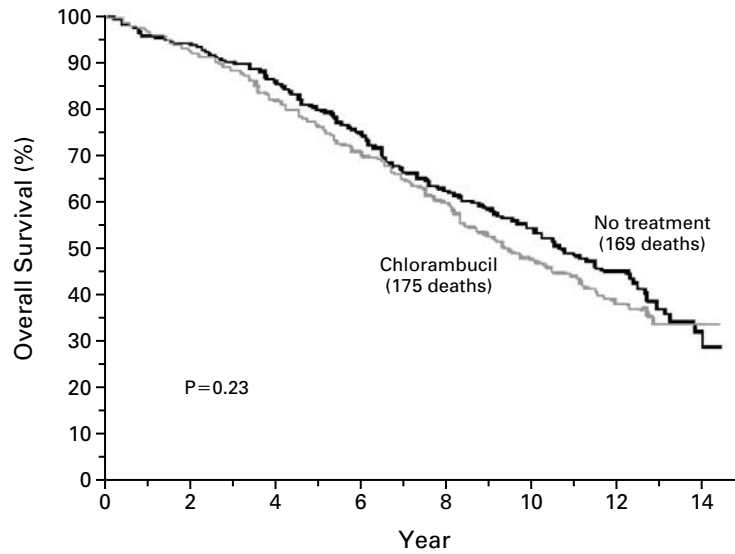
Table 3 shows the incidence of second neoplasms in the two groups. Forty-eight cancers were observed

in the untreated group (median interval between entry into the trial and the occurrence of the second cancer, 67 months; range, 6 to 165), as compared with 66 in the treated group (median interval, 72 months; range, 2 to 141) ($P=0.045$ by the chi-square test). Skin, mammary, and colon cancers and acute leukemia predominated in the treated group. Five of the six cases of leukemia in the two groups were of myeloid origin. The two cases of acute leukemia in the untreated group occurred in patients who were switched to chlorambucil five and nine years before the diagnosis of acute leukemia. The same phenomenon was observed in six of the nine patients with skin cancer in the untreated group.

The Second Trial

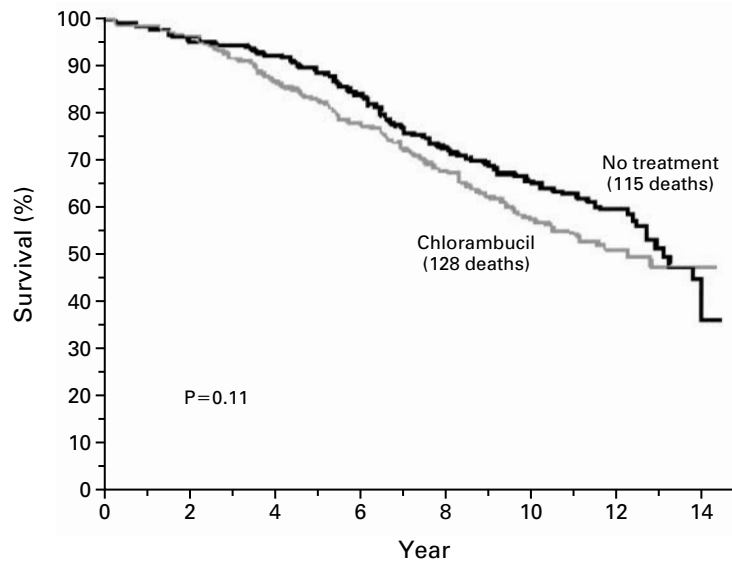
In the second trial, 247 deaths were recorded (Fig. 3), 126 in the untreated group (five-year survival, 81 percent; seven-year survival, 69 percent) and 121 in the treated group (five-year survival, 81 percent; seven-year survival, 69 percent; relative risk of death, 0.96; 95 percent confidence interval, 0.75 to 1.23; $P=0.74$ by the log-rank test).

In the untreated group, 25 of the 126 deaths were unrelated to CLL, 19 were caused by a second neoplasm, and no cause was identified in 17. Death was related to CLL in 65 patients (due to disease progression in 37, infection in 23, iatrogenic causes in 2, and thrombocytopenia in 3). In the treated group, 39 of the 121 deaths were unrelated to CLL, 18 were related to cancer, no cause was identified in 17, and 47 were related to CLL (due to disease progres-



No. AT RISK	
Chlorambucil	301 296 283 277 264 246 230 205 191 179 132 86 54 26 2
No treatment	308 291 284 266 247 230 213 196 179 159 114 70 39 17 7

Figure 1. Overall Survival in the First Trial.
The log-rank test was used to calculate the P value.



No. AT RISK	
Chlorambucil	301 296 284 277 264 246 230 205 191 179 132 86 54 26 2
No treatment	308 291 283 266 247 230 213 196 179 159 114 70 39 17 7

Figure 2. Kaplan–Meier Estimates of Mortality Due to CLL-Related Causes, Second Cancers, and Unknown Causes in the First Trial.
The log-rank test was used to calculate the P value.

TABLE 3. INCIDENCE OF SECOND CANCERS IN THE TWO TRIALS ACCORDING TO TREATMENT ASSIGNMENT.

SITE OR TYPE OF CANCER	FIRST TRIAL		SECOND TRIAL	
	NO TREATMENT	DAILY CHLORAMBUCIL	NO TREATMENT	CHLORAMBUCIL PLUS PREDNISONE
	no. of cases			
Skin	9	17	13	4
Mammary	1	7	3	4
Colon	3	7	2	6
Acute leukemia*	2	4	0	1
Lung	4	4	7	5
Prostate	8	5	7	7
Bladder	2	3	2	0
Oral	2	1	1	1
Pharynx and larynx	1	4	0	0
Pancreas	2	0	2	0
Kidney	2	1	2	1
Disseminated	2	1	1	0
Other	3	8	8	11
Unknown	7	4	2	2
Total	48	66	50	42

*There were three cases of acute myeloblastic leukemia type 2, one case each of type 3 and type 5, one case of type 2 following myelodysplasia, and one case of acute plasmacytic leukemia.

sion in 20, infection in 24, and thrombocytopenia in 3). There was no significant difference in overall survival after the exclusion of deaths unrelated to CLL ($P=0.16$ by the log-rank test) (Fig. 4).

The median follow-up was five years less than that of the first trial. As shown in Table 3, there were 50 second neoplasms in the untreated group (median interval from entry into the trial to the occurrence of a second cancer, 42 months; range, 1 to 104), as compared with 42 in the treated group (median interval, 30 months; range, 1 to 100) ($P=0.42$ by the chi-square test).

Response to Treatment and Disease Progression

The First Trial

In the first trial, the response to treatment could be evaluated in 278 of the 293 patients in the treated group who were alive at nine months. Of these 278 patients, 125 had complete responses (45 percent), 86 (31 percent) had partial responses, and 67 (24 percent) had no response to treatment. Among patients with complete responses and partial responses, the respective seven-year survival rates were 78 percent and 69 percent, as compared with a rate of 50 percent for patients with no response to therapy. Rai stage 0, Binet stage A',¹⁹ and fewer areas with enlarged lymph nodes were selected by a Cox model (data not shown) as predictive of a therapeutic response.

The Second Trial

In the second trial, the response to treatment could be evaluated in 437 of the 453 patients in the treated group who were alive at six months. Of these 437 patients, 124 (28 percent) had complete responses, 179 (41 percent) had partial responses, and 134 patients (31 percent) had no response to treatment. Among patients with complete responses and partial responses, the respective seven-year survival rates were 84 percent and 77 percent, as compared with a rate of 58 percent for patients who had no response to therapy. Rai stage 0, Binet stage A', lower initial lymphocyte count, and fewer areas with enlarged lymph nodes were selected by a Cox model (data not shown) as predictive of a therapeutic response.

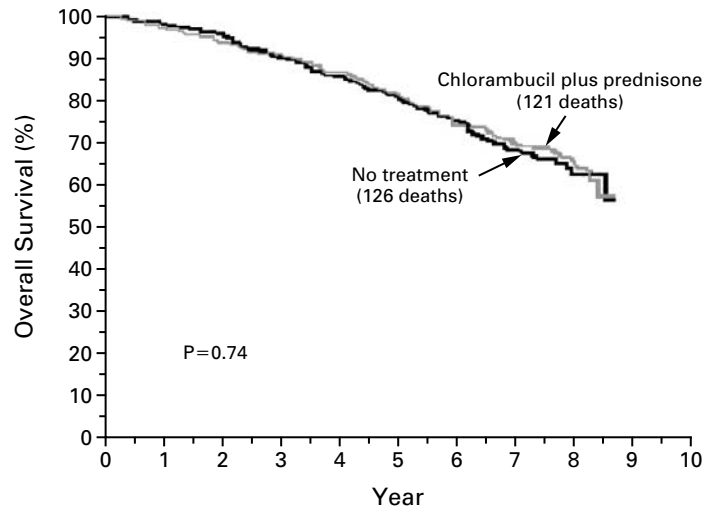
Both Trials

Figure 5 shows that in both trials disease progression occurred in significantly more patients in the untreated group than in the treated group. Progression to stage B occurred in 67 and 85 patients, respectively, in the untreated groups of the first and second trials, as compared with 38 and 41 patients in the treated groups of the two protocols. The survival of the untreated patients after progression to stage B (five-year survival, 56 percent in the first trial and 52 percent in the second trial) was similar to the survival of patients with stage B at presentation who received the same therapy in portions of the two trials devoted to the study of patients with stage B CLL.^{20,21} With respect to the proportion of patients with progression to stage C, there were no major differences between the untreated and treated groups in either trial. A minority of the untreated patients with progression to stage B (22 of 67 in the first trial and 22 of 85 in the second trial) were crossed over to therapy, whereas most of the untreated patients with progression to stage C (64 of 81 in the first trial and 67 of 84 in the second trial) were crossed over to therapy, and in some of these patients, CLL had previously evolved to stage B. Thus, the absence of a difference in the rate of progression to stage C might reflect resistance to chemotherapy in these patients.

Modifications of the Therapeutic Schedule

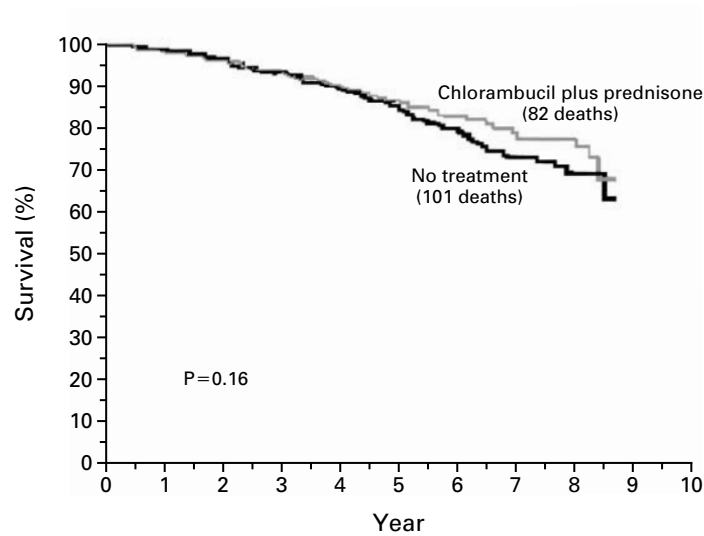
The First Trial

Among the 308 patients who were assigned to receive no treatment in the first trial (Table 4), 158 ultimately received treatment (110 received daily chlorambucil, 13 intermittent chlorambucil plus prednisone, 15 COP, 4 CHOP, 8 other combinations of chemotherapy, 6 corticosteroids, and 1 splenic irradiation, and 1 underwent splenectomy). Of these 158 patients, 97 were treated despite remaining in stage A, 44 because of progression to stage B, and



No. AT RISK	0	1	2	3	4	5	6	7	8	9	10
Chlorambucil plus prednisone	460	446	434	415	376	294	208	110	38		
No treatment	466	455	444	420	81	299	202	104	33		

Figure 3. Overall Survival in the Second Trial. The log-rank test was used to calculate the P value.



No. AT RISK	0	1	2	3	4	5	6	7	8	9	10
Chlorambucil plus prednisone	460	446	434	415	376	294	208	110	38		
No treatment	466	455	444	420	381	299	202	104	33		

Figure 4. Kaplan–Meier Estimates of Mortality Due to CLL-Related Causes, Second Cancers, and Unknown Causes in the Second Trial. The log-rank test was used to calculate the P value.

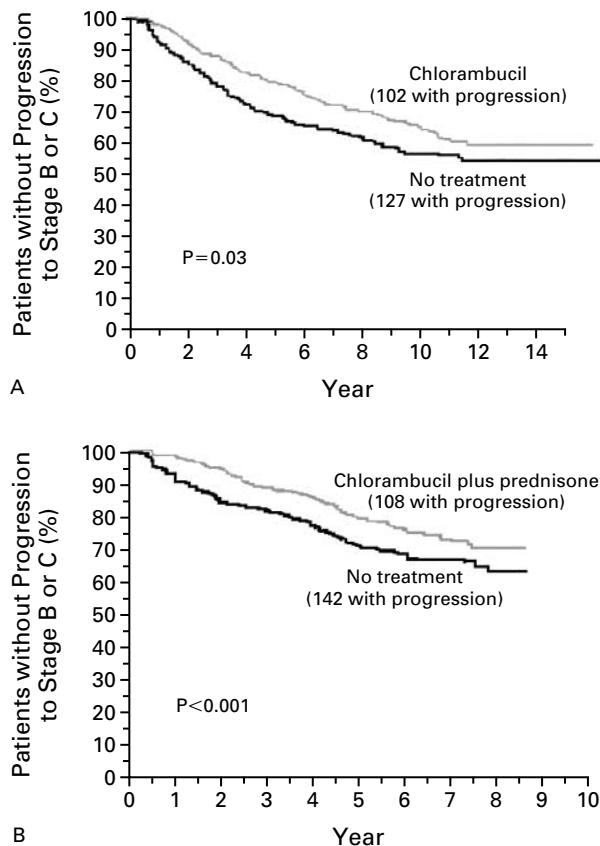


Figure 5. Patients without Progression to Stage B or C in the First Trial (Panel A) and the Second Trial (Panel B). The log-rank test was used to calculate the P value.

17 because of progression to stage C. In the group assigned to daily chlorambucil, 83 of the 301 patients were changed to another therapy (13 received chlorambucil plus prednisone, 24 COP, 20 CHOP, 22 other combinations of chemotherapy, and 4 corticosteroids). Treatment was changed in 28 patients even though they remained in stage A, in 14 because of progression to stage B, and in 41 because of progression to stage C.

The Second Trial

Among the 466 patients assigned to receive no therapy in the second trial, 187 received treatment (137 received chlorambucil plus prednisone, 20 CHOP, 14 daily chlorambucil, 14 other combinations of chemotherapy, 1 corticosteroids, and 1 total irradiation). Of these, 107 were given treatment despite remaining in stage A, 63 because they had progression to stage B, and 17 because they had progression to stage C. Among the treated patients, 97 were changed to another treatment (37 to CHOP, 28 to daily chlorambucil, 24 to other combinations

of chemotherapy, 6 to corticosteroids, 1 to splenectomy, and 1 to splenic irradiation). Treatment was changed in 53 patients even though they remained in stage A, in 18 because of progression to stage B, and in 26 because of progression to stage C. In both trials, the intention-to-treat analysis included all patients who were treated even though they remained in stage A.

DISCUSSION

A major issue in the management of indolent CLL (stage A) is whether deferring treatment is a reasonable alternative to immediate therapy. Our two trials, with more than 11 and 6 years of follow-up on 1535 patients, addressed this question. We found that daily chlorambucil alone or intermittent treatment with chlorambucil and prednisone did not prolong survival in patients with indolent CLL. Since deferring therapy until the disease progressed to stage B or stage C did not compromise survival, initial therapy could have been appropriately postponed.

Given daily or intermittently, alone or combined with corticosteroids, chlorambucil is the most commonly used drug in CLL.^{8-11,22} Although one study reported¹² that high doses of chlorambucil (15 mg per day until there was complete remission) were efficacious in advanced CLL, our results and previous reports from our group concerning stage A⁷ and stage B²⁰ CLL, together with the results of Shustik et al.¹⁰ and Catovsky et al.,⁹ demonstrate that the early use of chlorambucil does not influence survival in CLL.

In the absence of curative therapy, there are advantages to deferring treatment for patients with stage A CLL (63 percent of all patients with CLL have stage A disease). Postponing treatment avoids the side effects of cytotoxic therapy, including the infectious complications related to myelosuppression and the need for stringent follow-up. However, some patients who are concerned about their disease may want treatment, even in the absence of disease progression.

Although chlorambucil has been reported to induce secondary acute leukemia in patients treated for polycythemia vera²³ and when used as an immunosuppressive agent,²⁴⁻²⁷ this complication has not been reported in patients with CLL. In our series there were six cases of acute leukemia among the 422 patients who received daily chlorambucil as initial or secondary treatment, as compared with no cases among the 145 patients who never received therapy (Table 3).

An unexpected finding that emerged from the early results of the first trial was the relatively high frequency of epithelial neoplasms in the group treated with chlorambucil. This was subsequently found in three successive interim analyses (33, 50, and 66 cancers in the treated group at the third, fourth, and fifth

TABLE 4. ADDITIONAL TREATMENT GIVEN AND STAGE AT THE TIME OF THE CHANGE IN TREATMENT, ACCORDING TO TREATMENT ASSIGNMENT IN THE FIRST TRIAL.

VARIABLE	NO TREATMENT (N=158)			DAILY CHLORAMBUCIL (N=83)		
	STAGE A	PROGRESSION TO STAGE B	PROGRESSION TO STAGE C	STAGE A	PROGRESSION TO STAGE B	PROGRESSION TO STAGE C
No. of patients	97*	44	17	28†	14	41
No. of deaths	52	31	10	19	13	35
Interval between study entry and change in treatment (mo)						
Median	32	22	36	62	44	66
Range	5-148	5-134	3-108	9-146	14-127	3-142
Survival 9 yr after randomization (%)	61	54	33	45	21	27

*Treatment was started because of increased lymphocytosis or lymphadenopathy in 61 patients and causes unrelated to disease progression in 36 patients.

†Treatment was changed because of increased lymphocytosis or lymphadenopathy in 20 patients and causes unrelated to disease progression in 8 patients.

interim analyses, respectively, as compared with 19, 25, and 48 cancers in the untreated group). However, these differences are not significant ($P=0.045$), and they were not confirmed in the second trial. Nevertheless, we cannot rule out an oncogenic potential of chlorambucil because the total dose of chlorambucil differed in the two trials (3 mg per kilogram per month vs. 1.5 mg per kilogram when given intermittently), as did the duration of treatment (long-term continuous therapy vs. three years of therapy) and the timing of therapy (daily vs. intermittent).

Our results indicate that chlorambucil can delay disease progression, even though it does not affect survival. We cannot rule out the possibility that patients in the treated groups with progression to stage B had a poorer initial prognosis. However, the differences in survival nine years after randomization (Table 4) between untreated patients with progression to stage B and treated patients with progression to stage B (54 percent vs. 21 percent) suggest that early exposure to the drug selects for resistant clones, which are the cause of the poor prognosis of patients who have no response to early therapy.

Of the 308 patients in the first trial who were not treated, 49 percent remained in stage A and needed no therapy after follow-up of more than 11 years. However, 27 percent of the untreated patients in stage A died of causes related to the disease, and more than half began therapy because the disease began to progress.

Our results emphasize the need for both a better definition of stage A CLL and curative treatment for indolent CLL, particularly in young patients. There is evidence that purine analogues, particularly fludarabine, are the most effective agents for this disorder.²⁸⁻³⁰ Since these drugs have not been shown to

improve overall survival, it is premature to recommend them for patients with stage A CLL, particularly in stage A', since survival in patients with stage A' disease is close to that of a sex-matched and age-matched normal population. However, young patients with stage A'' CLL, whose five-year survival rate is 62 percent,⁷ may be candidates for treatment with these drugs.

We are indebted to Professor Jacques Benichou (Centre Hospitalier Universitaire de Rouen) for his invaluable help in revising the manuscript.

APPENDIX

The following institutions (all in France unless otherwise specified) and members of the French Cooperative Group on Chronic Lymphocytic Leukemia were involved in the two trials: Centre Hospitalier Régional, Lille: P. Fenaux, P. Morel; Centre Henri Becquerel, Rouen: H. Piguet, M. Monconduit, F. Tilly; Hôpital Sud, Amiens: J.-F. Claisse; Hôpital Robert Debré, Reims: J.-C. Adjizian, G. Potron, B. Pignon; Centre Hospitalier Régional, Caen: X. Troussard, O. Reman; Groupe Hospitalier Pitié-Salpêtrière, Paris: H. Merle-Béral; Centre Hospitalier Régional, Tours: M. Reisenleiter, C. Linassier, J.-P. Lamagnère; Hôpital Nord, Saint-Etienne: C. Vasselom; Hôpital Sud, Rennes: D. Jacomy, B. Grosbois; Hôpital La Milletterie, Poitiers: F. Guilhot; Hôpital de la Source, Orléans: G. Vaugier; Hôpital de la Durance, Avignon: P. Souteyrand, G. Lepeu, A.-M. Touchais; Hôpital Mustapha, Algiers, Algeria: N. Boudjerra; Centre Hospitalier Régional, Limoges: M. Bordessoule; Hôtel-Dieu, Clermont-Ferrand: O. Tournilhac; Centre Départemental de Transfusion Sanguine, Pontoise: J. Facquet-Danis; Hôpital Edouard-Herriot, Lyons: C. Sebban; Centre Hospitalier, Meaux: C. Allard; Centre Hospitalier Régional, Montpellier: B. Murgue; Centre Hospitalier, Nîmes: J.-F. Schved, A. Arnaud; Hôpital Avicenne, Bobigny: P. Cassassus; Hôpital de Pontchaillou, Rennes: P.-Y. Le Prisé; Centre Hospitalier, Antibes: J.-F. Dor; Hôpital Antoine Béclère, Clamart: P. Solal-Celigny, G. Tchernia; Hôpital Beaujon, Clichy: J.-F. Bernard; Hôpital Saint-Joseph, Paris: J.-M. James; Centre Hospitalier, Vichy: A. Reigner; Centre Hospitalier, Chambéry: M. Blanc; Centre Hospitalier Régional, Nantes: M.-J. Rapp; Centre Hospitalier, Evreux: J.-P. Bourgeois; Hôpital Jean Verdier, Bondy: F. Lejeune; Centre Hospitalier, Chalon-sur-Saône: B. Salles; Centre Hospitalier de la Côte Basque, Bayonne: M. Renoux; Hôpital Jules Courmont, Lyons: B. Garin; Centre Hospitalier Maréchal Joffre, Perpignan: J. Camo; Hôpital Robert

Boulin, Libourne: J. Ceccaldi; Centre Hospitalier, Corbeil: A. Devidas; Centre René Gauducheau, Nantes: A. Le Mevel-Le Pourhiet; Centre Hospitalier Régional, Brest: J. Brière; Centre Hospitalier, Saint-Germain en Laye: M. Janvier; Hôpital Saint-Louis, Paris: Y. Najean; and Hôpital Saint-Louis, Paris: C. Chastang and S. Chevret (statisticians), D. Meffre and C. Dumont (monitors).

REFERENCES

1. Dighiero G, Travade P, Chevret S, et al. B-cell chronic lymphocytic leukemia: present status and future directions. *Blood* 1991;78:1901-14.
2. Rozman C, Montserrat E. Chronic lymphocytic leukemia. *N Engl J Med* 1995;333:1052-7. [Erratum, *N Engl J Med* 1995;333:1515.]
3. Rai K, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34.
4. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood* 1996;87:4990-7.
5. International Workshop on Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. *Ann Intern Med* 1989;110:236-8.
6. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981;48:198-206.
7. The French Cooperative Group on Chronic Lymphocytic Leukemia. Effects of chlorambucil and therapeutic decision in initial forms of chronic lymphocytic leukemia (stage A): results of a randomized clinical trial on 612 patients. *Blood* 1990;75:1414-21.
8. Sawitsky A, Rai KR, Glidewell O, Silver RT. Comparison of daily versus intermittent chlorambucil and prednisone therapy in the treatment of patients with chronic lymphocytic leukemia. *Blood* 1977;50:1049-59.
9. Catovsky D, Richards S, Fooks J, Hamblin TJ. CLL trials in the United Kingdom: MRC trials 1, 2 and 3. *Leuk Lymphoma* 1991;5:Suppl 4:105-11.
10. Shustik C, Mick R, Silver R, Sawitsky A, Rai K, Shapiro L. Treatment of early chronic lymphocytic leukemia: intermittent chlorambucil versus observation. *Hematol Oncol* 1988;6:7-12.
11. Begleiter A, Mowat M, Israels LG, Johnston JB. Chlorambucil in chronic lymphocytic leukemia: mechanisms of action. *Leuk Lymphoma* 1996;23:187-201.
12. Jaksic B, Brugiatielli M. High dose continuous chlorambucil vs intermittent chlorambucil plus prednisone for treatment of B-CLL — IGCI CLL-01 trial. *Nouv Rev Fr Hematol* 1988;30:437-42.
13. Jaksic B, Brugiatielli M, Krc I, et al. High dose chlorambucil versus Binet's modified cyclophosphamide, doxorubicin, vincristine, and prednisone regimen in the treatment of patients with advanced B-cell chronic lymphocytic leukemia: results of an international multicenter randomized trial: International Society of Chemo-Immunotherapy, Vienna. *Cancer Ther* 1996;38:Suppl 2:S41-S63.
14. Dighiero G, Binet JL. Chronic lymphocytic leukemia. *Hematol Cell Ther* 1996;38:Suppl 2:S41-S63.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
16. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc [A]* 1972;135:185-206.
17. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-202.
18. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977;64:191-9.
19. The French Cooperative Group on Chronic Lymphocytic Leukaemia. Natural history of stage A chronic lymphocytic leukaemia untreated patients. *Br J Haematol* 1990;76:45-57.
20. *Idem*. A randomized clinical trial of chlorambucil versus COP in stage B chronic lymphocytic leukemia. *Blood* 1990;75:1422-5.
21. *Idem*. Is the CHOP regimen a good treatment for advanced CLL? Results from two randomized clinical trials. *Leuk Lymphoma* 1994;13:449-56.
22. Catovsky D, Fooks J, Richards S. The UK Medical Research Council CLL trials 1 and 2. *Nouv Rev Fr Hematol* 1988;30:423-7.
23. Berk PD, Goldberg JD, Silverstein MN, et al. Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *N Engl J Med* 1981;304:441-7.
24. Kauppi MJ, Savolainen HA, Anttila VJ, Isomaki HA. Increased risk of leukaemia in patients with juvenile chronic arthritis treated with chlorambucil. *Acta Paediatr* 1996;85:248-50.
25. Dedrick RL, Morrison PF. Carcinogenic potency of alkylating agents in rodents and humans. *Cancer Res* 1992;52:2464-7.
26. Patapanian H, Graham S, Sambrook PN, et al. The oncogenicity of chlorambucil in rheumatoid arthritis. *Br J Rheumatol* 1988;27:44-7.
27. Palmer RG, Denman AM. Malignancies induced by chlorambucil. *Cancer Treat Rev* 1984;11:121-9.
28. Keating MJ, Kantarjian H, Talpaz M, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. *Blood* 1989;74:19-25.
29. Johnson S, Smith AG, Löffler H, et al. Multicentre prospective randomized trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. *Lancet* 1996;347:1432-8.
30. Rai KR, Peterson B, Elias L, et al. A randomized comparison of Fludarabine and Chlorambucil for patients with previously untreated chronic lymphocytic leukemia: a CALGB, SWOG, CTG/NCI-C and ECOG Inter-Group study. *Blood* 1996;88:Suppl 1:141a. abstract.