A Randomized Clinical Trial of Chlorambucil Versus COP in Stage B Chronic Lymphocytic Leukemia

By the French Cooperative Group on Chronic Lymphocytic Leukemia

In 1980, the French Cooperative Group on Chronic Lymphocytic Leukemia started a randomized clinical trial in which intermediate prognosis patients (stage B) received either an indefinite course of chlorambucil (0.1 mg/kg/d) or 12 cycles of the COP regimen (vincristine, cyclophosphamide, and prednisone). We present the results of the third interim analysis based on 291 patients (151 in the chlorambucil group and 140 in the COP group) with a mean follow-up of 53 months at the reference date of June 1, 1987. At this date, 129 deaths were observed, 65 in the chlorambucil group and 64 in the COP group; there was no improvement in overall survival with the COP regimen (P = .44) even after adjusting for both prognostic and imbalanced factors (P = .24). The 3-year and 5-year overall survival rates were, respectively, 69% and 44% in the chlorambucil group as compared with 73% and 43% in the COP group. The median survival times were 58 months in the chlorambucil group and 57 months in the COP group. Moreover, no significant difference was observed between the two treatment groups in terms of either treatment response, 9-month status, time to disease progression to stage C, or causes of death.

© 1990 by The American Society of Hematology.

Until 1975, prognosis of chronic lymphocytic leukemia (CLL) was considered unpredictable. At that time, Rai et al 1 made a substantial contribution to the understanding of prognosis by defining a five-stage clinical system, whose prognosis significance has been widely confirmed. In 1979 we devised a three-stage (A, B, C) clinical system derived from the use of Cox’s model on a retrospective and on a prospective series. 2 This staging system has been validated since and has succeeded in better separating good (stage A) from intermediate (stage B) prognosis CLL patients. 3,4 Stage A is defined by hemoglobin ≥ 100 g/L, platelet count ≥ 100 x 10^9/L and less than three involved areas (counting as one cervical, axillary, and inguinal lymph nodes, whether unilateral or bilateral, the spleen, and the liver). It accounts for 60% of all CLL patients and the 5-year survival rate is 78%. 5 It comprises all Rai’s stage 0 patients, two thirds of Rai’s stage I patients, about one third of Rai’s stage II patients, and one sixth of Rai’s stage III patients. 5 Stage B is defined by hemoglobin ≥ 100 g/L, platelet count ≥ 100 x 10^9/L, and at least three involved areas. It accounts for 30% of all CLL patients and the 5-year survival rate is 44%. 6 It comprises about one third of Rai’s stage I patients, about two thirds of Rai’s stage II patients, and about one half of Rai’s stage III patients. 5

In May 1980, the French Cooperative Group on CLL started a clinical trial in which stage B patients were randomized to receive either daily chlorambucil or 12 courses of the polychemotherapy COP (vincristine, cyclophosphamide, and prednisone). Accrual in this trial was stopped in May 1985. The first interim analysis, based on 226 patients with a mean follow-up of 22 months, failed to show any benefit with COP. 6 We present the results of the third interim analysis, based on June 1, 1987, as the reference date. They are based on 291 patients whose mean follow-up is 53 months.

Patients and Methods

Criteria for eligibility. Diagnosis of CLL was performed on the basis of peripheral lymphocytosis (greater than 10 x 10^9/L or a minimum of 4 x 10^9/L for at least the three previous months), combined with bone marrow lymphocyte infiltration (defined by more than 30% of lymphocytes in aspirates). Patients who had not been previously treated for CLL and who were classified as stage B according to the (A, B, C) staging system were eligible for this trial. Stage C patients (defined by hemoglobin < 100 g/L or platelet count < 100 x 10^9/L older than 80 years were randomized as stage B patients. Those patients with an associated neoplasia, a positive Coombs test, or a prolymphocytic leukemia were excluded. The protocol was approved by the ethics committee of the Groupe Hospitalier Pitit-Salpêtrière (Paris, France), but written informed consent was not required according to French regulations in effect at the time.

Randomization and treatment schedule. There were 31 participating centers and randomization was performed through a centralized telephone assignment procedure according to stage. Stage B patients were randomly allocated either to chlorambucil at the daily oral dose of 0.1 mg/kg given indefinitely or to 12 courses (one per month for 6 months, then one every 3 months for 18 months) of COP, consisting of vincristine, 1 mg/m^2 given intravenously on day 1 of each course; oral prednisone, 40 mg/m^2 on days 1 to 5, and cyclophosphamide at the oral dose of 300 mg/m^2 on days 1 to 5. After receiving 12 courses of COP regimen, patients in the COP group were given an indefinite course of chlorambucil at the daily oral dose of 0.1 mg/kg. The treatment was not blind. Dose reductions of 50% were made whenever neutrophil count fell to 1.0 to 1.5 x 10^9/L or platelet count fell to 50 to 100 x 10^9/L, and chemotherapy was interrupted whenever neutrophils dropped to less than 1 x 10^9/L or platelets to less than 50 x 10^9/L. As these counts rose, normal dosage of chemotherapy was resumed. If disease progression to stage C was observed within the first 9 months after randomization, initial treatment was carried on. If disease progression to stage C was observed after the first 9 months, a more aggressive treatment was given: COP in the chlorambucil group and the polychemotherapy CHOP, consisting of COP and doxorubicin, in the COP group.

Follow-up examinations. Follow-up examinations were scheduled for the ninth month and every 6 months thereafter. Each included a clinical examination, complete blood count, blood sedimentation rate, Coombs test, immuno-electrophoresis, and quantitation.
of immunoglobulins. Medullary aspiration and medullary biopsy were recommended, especially in patients undergoing clinical and hematologic remission.

Endpoints. The main endpoint was overall survival from the date of randomization. Disease progression to stage C, stage at the ninth month according to the (A, B, C) classification, and remission status at the ninth month (clinical and hematologic remission, partial remission, stabilization, progression) were also analyzed. Clinical and hematologic remission were characterized by lymphocyte count < 4 x 10^9/L, hemoglobin > 120 g/L, platelet count > 150 x 10^9/L, and neither adenopathy, splenomegaly, or hepatomegaly. Partial remission was defined by a decrease of at least 50% in the diameter of the involved lymph nodes and a decrease of at least 75% in the lymphocyte count, both compared with the initial examination. Disease progression was defined as either progression to stage C, increase in lymphocyte count, or increase in tumoral mass. The absence of both remission and progression defined stabilization.

Estimation of sample size. Estimation of sample size was based on the method described by George and Desu, with an expected annual accrual of 100 CLL patients (52% in stage A, 34% in stage B, and 14% in stage C) based on previous series, a type I error of $\alpha = 0.05$, a type II error of $\beta = 0.10$ for a one-sided test, and a hypothesis of treatment benefit given by an increase in 1-year survival from 90% with chlorambucil to 95% with COP. It was computed that 282 stage B patients had to be recruited in 8.3 years to observe the required number of events; ie, 66 deaths. Five interim analyses were planned at a level of $\alpha = 0.016$ to maintain an overall level of $\alpha = 0.05$.

Statistical analysis. Analysis was made on an intention-to-treat basis. Survival analysis was based on the Kaplan-Meier estimate, the log-rank test, and Cox's regression model. The findings at the reference date of June 1, 1987 were used. Treatment comparison used a one-sided test as the assumption was a benefit from the COP polychemotherapy.

RESULTS

From May 27, 1980 to May 31, 1985, 289 stage B patients and 2 stage C patients older than 80 years were recruited and randomized to receive either daily chlorambucil (151 patients) or COP regimen (140 patients). The mean follow-up was 53 months. Four patients were lost to follow-up, two in each group, and 129 died.

The main characteristics of the two treatment groups are presented in Table 1. While there are some imbalances (more males, more patients with infections or with general symptoms in the chlorambucil group), this table shows no major differences in the distribution of clinical and biologic parameters in the two treatment groups. For all patients, mean age was 63 years, mean number of involved areas was 3.6, mean lymphocyte count was 54 x 10^9/L, mean hemoglobin level was 134 g/L, mean platelet count was 210 x 10^9/L, and mean lymphocyte bone marrow infiltration in aspirates was 73%.

Among the 129 deaths, 65 occurred in the chlorambucil group and 64 in the COP group (Fig 1: $P = 0.435$, one-sided log-rank test). The 3-year and 5-year survival rates were, respectively, 69% with a standard deviation (SD) of 4% and 44% (SD = 5%) in the chlorambucil group as opposed to 73% (SD = 4%) and 43% (SD = 6%) in the COP group; the median survival time was 58 months in the chlorambucil group and 57 months in the COP group. Moreover, treatment comparison was adjusted for seven parameters selected as either being imbalanced between the two groups or as being individually predictive for overall survival using Cox's model, namely sex, general symptoms, infection, number of involved areas, Karnofsky index, bone marrow infiltration, and size of involved areas (with two levels, one defined by the presence of either splenomegaly with the spleen palpable under the umbilicus or at least one lymph node ≥ 4 cm, and the other level by none of those signs). The adjusted treatment comparison showed no difference in survival between the two groups ($P = 0.24$; one-sided, log-likehood ratio test). Finally, there was no difference between the two treatment groups for the causes of death (Table 2).

At the 9-month follow-up examination, remission status (clinical and hematologic remission, partial remission, stabilization, and progression) was not different between the two groups ($P = 0.41$, 3 degrees of freedom [df] chi square test). Clinical and hematologic remission was observed for 20 patients in the chlorambucil group as opposed to 28 in the COP group (Table 3). The 3-year survival rates were 96%, 81%, 68%, and 30% in patients with clinical and hematologic remission, partial remission, stabilization, and progression, respectively. Stage at the ninth month was not different between the two treatment groups ($P = 0.81$, 2 df chi square test). Eighty patients (58%) in the chlorambucil group evolved to stage A as compared with 78 (61%) in the COP group, while 12 patients (9%) in the chlorambucil group and 9 (6%) in the COP group progressed to stage C. Finally, no
difference was observed for time to disease progression to stage C between the two groups (Fig 2): 44 patients in the chlorambucil group and 39 in the COP group evolved to stage C ($P = .40$; one-sided logrank test) before the reference date.

**DISCUSSION**

This trial in stage B was part of the CLL 80 protocol in which two other trials were run simultaneously. Stage A patients were randomized between no treatment and daily chlorambucil, and stage C patients were randomized between the polychemotherapies COP and CHOP. Accrual of new patients was terminated in the whole CLL 80 protocol with the results of the first interim analysis, the reference date of which was May 1, 1984. The decision was based on the evidence of a treatment benefit in stage C and on the higher than expected accrual rate. However, at the time of first interim analysis, the power of the treatment comparison to detect an increase in 1-year survival from 90% with chlorambucil to 95% with COP was only 75% in stage B given the number of deaths (d = 42). This third interim analysis is now based on 291 patients with a longer follow-up (53 months on average), and the power of treatment comparison is now 99% given the number of deaths (d = 129). Therefore, the nonsignificant result observed cannot be attributed to lack of power.

Chlorambucil was first introduced for the treatment of CLL in 1952, and has been the most common treatment used in CLL since, either on daily continuous regimen or on intermittent high dose schedules. A response rate of 60% with 10% to 20% of complete remission has been reported in several trials, but these results failed to be conclusive given the absence of well-defined criteria for patients' selection, such as clinical staging, and the small sample sizes. Indeed, there has not been any randomized trial including homogeneous groups of CLL patients indicating a beneficial role of chlorambucil in terms of survival. Recently, our group failed to show any significant benefit of chlorambucil in stage A patients when compared with no treatment. The only well-accepted notion emerging from past trials is the prognostic value of response to chlorambucil, which we confirm in the present trial, since an unfavorable outcome is observed in the absence of response and a significant improvement in survival is observed for patients achieving clinical and hematologic or partial responses. However, it is well-known that such results only show an association between response and survival, which may have no relevance to the efficacy of treatment.

COP has been reported an effective and well-tolerated regimen in advanced CLL. However, these results were not confirmed in a nonrandomized trial or in a randomized trial conducted by the Spanish Cooperative Group PETHEMA. More recently, the PETHEMA group found that the polychemotherapy CMP (cyclophosphamide, melphalan, and prednisone) did not display better results in terms of overall survival or response to treatment than the usual intermittent chlorambucil-prednisone regimen in a randomized clinical trial of 96 patients (62 stage B patients and 34 stage C patients).

The Eastern Cooperative Oncology Group (ECOG) designed a trial where Rai's stages III or IV or symptomatic stage II were randomized between chlorambucil plus prednisone and cyclophosphamide, vincristine, and prednisone (CVP). No differences were observed.

**CONCLUSION**

Finally, since these results failed to show any improvement with COP in stage B and since we showed a significant improvement with CHOP as compared with COP in a randomized clinical trial in stage C, in 1985 we started a new randomized clinical trial in stage B comparing the classical intermittent chlorambucil plus prednisone schedule with CHOP. The Danish Group is also currently running a trial comparing almost the same treatments in stages B and C.

**APPENDIX**

**MEMBERS OF THE FRENCH COOPERATIVE GROUP ON CHRONIC LYMPHOCYTIC LEUKEMIA PROTOCOL CLL 80**

REFERENCES


5. French Cooperative Group on Chronic Lymphocytic Leukemia: Benefit of the “CHOP” regimen in advanced untreated chronic lymphocytic leukemia: Results from a randomized clinical trial. Lancet 1:1346, 1986

6. George SL, Desu MM: Planning the size and duration of a clinical trial studying the time to some critical event. J Chronic Dis 87:15, 1974


A randomized clinical trial of chlorambucil versus COP in stage B chronic lymphocytic leukemia. The French Cooperative Group on Chronic Lymphocytic Leukemia