EXHIBIT 2006

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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

The French Cooperative Group on Chronic Lymphocytic Leukemia

In a multicenter clinical trial conducted by the French Cooperative Group on Chronic Lymphocytic Leukemia (CLL) between June 1, 1990, and October 1, 1992, 183 patients with stage B CLL and 79 patients with stage C CLL were randomized to receive either cyclophosphamide/doxorubicin/prednisone (CAP) (71 stage B patients and 25 stage C patients), or cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) (56 stage B patients and 27 stage C patients), or fludarabine (FDB) (56 stage B patients and 27 stage C patients). The mean follow-up was 14 months (standard deviation, 7 months). At the 6-month follow-up examination, the results suggested that FDB was more effective than CAP and CHOP in patients with stage B disease (n = 183), with 19% of FDB-treated patients achieving "clinical and hematological remission" (CR) compared with 11% of the CHOP-treated patients and 7% of the CAP-treated patients (P = .08; 6 degrees of freedom; chi-squared test). The rates of partial remission (PR) and overall response (CR + PR) were, respectively, 75% and 94% for the FDB-treated patients, 64% and 75% for the CHOP-treated patients, and 65% and 72% for the CAP-treated patients. However, in patients with stage C CLL (n = 77) at entry to the study, the remission status at 6 months showed slightly greater improvement in the CAP-treated group (n = 25), in which 84% of patients achieved remission (CR + PR) compared with 64% of patients in the FDB-treated group (n = 27) and 63% of patients in the CHOP-treated group (n = 27). Further analysis of the study data may help to clarify the significance of these findings and to determine whether FDB improves survival in patients with advanced CLL.

IN JUNE 1990, the French Cooperative Group on Chronic Lymphocytic Leukemia (CLL) activated a multicenter randomized clinical trial in which Binet stage B and stage C CLL patients were allocated to receive either fludarabine (FDB) or one of two polychemotherapeutic regimens that included doxorubicin. We report the preliminary results of this trial, based on October 1, 1992, as the reference date.

MATERIALS AND METHODS

Diagnosis of CLL was based on the International Workshop on Chronic Lymphocytic Leukemia criteria.[1] Patients younger than 75 years who had not been previously treated and who were classified as stage B or C[2] were eligible for this trial. There were 51 participating centers, and randomization was performed through a centralized telephone assignment procedure according to stage. Follow-up examinations were scheduled for the third and sixth month after randomization, and every 6 months thereafter.

Patients were randomly allocated to receive either FDB 25 mg/m^2 intravenously (IV) daily for 5 days; cyclophosphamide 750 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, and prednisone 40 mg/m^2 orally on days 1 to 5 (CAP); or vincristine 1 mg/m^2 IV and doxorubicin 25 mg/m^2 IV on day 1 plus cyclophosphamide 300 mg/m^2 and prednisone 40 mg/m^2 orally on days 1 to 5 (CHOP). The first six courses of treatment were given at monthly intervals and the last six courses at 3-month intervals. In case of disease progression within the first 3 months after randomization, initial treatment was continued, but thereafter choice of treatment could be made according to the following rule. At 3 months, patients allocated to receive CAP or FDB who were considered to be treatment failures (see below) were switched to FDB or CAP, respectively. At 6 months, patients exhibiting disease progression were given FDB, with the exception of previous FDB treatment failures; reduction by 50% (doxorubicin dose) was made whenever remission was observed. Finally, all responders (see below) who received FDB at 6 months were randomized either to continuation for six courses or discontinuation of FDB.

The main endpoint was overall survival from the date of randomization. Remission status ("clinical and hematological remission" [CR], partial remission [PR], stable disease [SD], progressive disease [PD]) and stage at 6 months were also analyzed. Complete remission was defined by the absence of clinical signs, lymphocytosis less than 4×10^9/L, hemoglobin greater than 120 g/L, and platelets greater than 150×10^9/L; PR 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; PD was defined as either progression to stage C, increase in lymphocyte count, or increase in tumoral mass; and SD was defined as the absence of both remission and progression.

Statistical analysis (using SAS software; SAS Institute, Cary, NC) was made on an intention-to-treat basis based on the log-rank and the chi-squared tests.

RESULTS

From June 1, 1990, to October 1, 1992, 183 stage B patients and 79 stage C patients were re-

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cruited and randomized to receive either CAP (71 stage B patients and 25 stage C patients), CHOP (56 stage B patients and 27 stage C patients), or FDB (56 stage B patients and 27 stage C patients). The mean follow-up was 14 months (standard deviation, 7 months). At the reference date, 19 patients had died (five stage B patients and 14 stage C patients) and information was incomplete for 30 patients (22 stage B patients and eight stage C patients).

Although there were slight imbalances, no major difference in the distribution of clinical and biologic parameters was observed between treatment groups in each stage. In stage B and stage C patients, the mean age was 60 and 62 years, the mean lymphocyte count was 58×10^9/L and 112×10^9/L, the mean hemoglobin level was 133 g/L and 96 g/L, the mean platelet count was 192×10^9/L and 114×10^9/L, and the mean lymphocyte bone marrow infiltration was 73% and 84%, respectively.

Stage B Chronic Lymphocytic Leukemia

In the follow-up examination at 6 months, remission status (CR, PR, SD, and PD), assessed in 151 patients, differed between the three treatment groups, but not significantly ($P = .08$; 6 degrees of freedom; chi-squared test). Complete remission was observed in nine (19%) patients in the FDB-treated group compared with four (7%) in the CAP-treated group and five (11%) in the CHOP-treated group (Table 1). Moreover, stage at 6 months differed between the treatment groups ($P = .02$; 6 degrees of freedom; chi-squared test), with 39 (83%) of the 47 FDB-treated patients in stage A or in remission compared with 31 patients (54%) in the CAP-treated group and 27 patients (56%) in the CHOP-treated group.

Among the five deaths, three occurred in the CAP-treated group and two occurred in the CHOP-treated group ($P = .30$; 2 degrees of freedom; log-rank test).

Stage C Chronic Lymphocytic Leukemia

Remission status at 6 months was not different between the three groups ($P = .17$; 6 degrees of freedom; chi-squared test), although slight improvement could be observed in the CAP-treated group, with 84% patients exhibiting remission (CR or PR) compared with 64% in the FDB-treated group and 63% in the CHOP-treated group (Table 1). In terms of staging at the 6-month follow-up examination, differences were no longer observed between the three groups ($P = .94$; 6 degrees of freedom; chi-squared test), with 55% of the CAP-treated patients in stage A or in remission compared with 50% of patients in the FDB-treated group and 43% of patients in the CHOP-treated group.

Among the 14 deaths, five occurred in the CAP-treated group, four occurred in the CHOP-treated group, and five occurred in the FDB-treated group ($P = .73$; 2 degrees of freedom; log-rank test).

DISCUSSION

In advanced forms of CLL, the efficacy of FDB, a fluorinated analog of adenine, recently has been claimed,[3,4] with reported complete response rates ranging from 29% in previously treated CLL cases to 75% in previously untreated CLL cases; mild toxicity also has been reported. Unfortunately, these results were based on uncontrolled studies and, thus, no conclusion in terms of superiority of FDB could be demonstrated.

We report the short-term results of a multicenter, randomized clinical trial based on 262 stage B and C CLL patients comparing FDB with classically used CAP and CHOP regimens. Our results appear surprisingly controversial according to stage, and suggest that FDB is more effective than the polychemotherapy regimens containing anthracycline in stage B while CAP may be slightly superior in stage C. This may be ex-

Table 1. Response Status 6-Months Follow-up Examination According to Stage and Randomization

	Stage B (%)			Stage C (%)		
	CAP	CHOP	FDB	CAP	CHOP	FDB
CR	4 (7)	5 (11)	9 (19)	1 (5)	2 (8)	3 (14)
PR	37 (65)	30 (64)	35 (75)	15 (79)	13 (54)	11 (50)
SD	12 (21)	9 (19)	1 (2)	2 (11)	9 (38)	5 (23)
PD	4 (7)	3 (6)	2 (4)	1 (5)	—	3 (13)
		$P = .08$			$P = .17$	

plained by the distinct pathophysiology of this latter form of the disease.

However, even if FDB induces a higher response rate in stage B CLL, in agreement with previous results from Keating et al,[3,4] its effect on survival is still undetermined. Although correlation between treatment response and survival in CLL has been described, it was not analyzed in statistical terms, so that further analysis is warranted. Moreover, we are now segregating the "clinical and hematologic remissions" and the "biologic remissions" (defined by bone marrow biopsy, blood lymphocyte phenotypes, and immunoglobulin rearrangement). Finally, studies by our group and by other investigators have shown that, at least in stage B patients, the CHOP regimen improved response without improving survival. Whether this is explained through a selection process leading to the appearance of a resistant clone remains unclear. We hope this study is able, in the near future, to answer the question of whether FDB could improve survival in CLL cases.

APPENDIX

The members of the French Cooperative Group on Chronic Lymphocytic Leukemia (protocol CLL 90) include the Departments of Hematology and Physicians from the following institutions: CHU de Lilles (P. Fenaux); CHU Pitié-Salpétrière, Paris (J-L. Binet and K. Maloum); CHU de Caen (M. Leporrier); CHU de Nantes (M-J. Rapp); Centre Henri Becquerel, Rouen (H. Piguet); CHU de Besançon (A. Brion); Hôpital Mustapha, Alger (N. Boudjerra); Poitiers (B. Dreyfus); Hôpital Sud, Rennes (R. Leblay); Institut Paoli Calmettes, Marseille (A-M. Stoppa); Hôpital du Morvan, Brest (J-P. Autrand); Hôpital Edouard Herriot, Lyon (C. Sebban); CHU Brabois, Nancy (J-F. Paitel); Hôpital de La Roche-sur-Yon (P. Maisonneuve); Hôpital Lapeyronic, Montpellier (T. Rousset); Hôpital Bretonneau, Tours (M. Linassier); Hôpital Saint-Louis, Paris (P. Brice); Hôtel-Dieu, Clermont-Ferrand (Ph. Travade); Hôpital Henri-Mondor, Créteil (M. Divine); CHU d'Amiens (B. Desablens); Hôpital Nord, Saint-Etienne (J. Jaubert); Hôpital de Meaux (C. Allard); Hôpital Saint-Antoine, Paris (D. Cheron); Fondation Bergonié, Bordeaux (J-P. Eghbali); Centre Jean Bernard, Le Mans (Ph. Solal Celigny); CHU de Limoges (D. Bordessoule); Hôpital Robert Debré, Reims (B. Pignon); Hôpital d'Orléans (G. Vaugier); Hôpital Jean Verdier, Bondy (F. Lejeune); Hôpital de Chalon-sur-Saône (B. Salles); Centre Henri Dunan, Corbeil (M. Devidas); Hôpital de Chambéry (M. Blanc); Hôpital Jeanne Delanoue, Saumur (M. Maigre); Hôpital de Vichy (A. Reigner); Hôtel-Dieu, Valenciennes (Ph. Simon); Hôpital de Bon Secours, Metz (B. Christian); CHU de Nimes (J-F. Schved); Hôpital Antoine Béclère, Clamart (P. d'Oiron); Hôpital de Blois (M. Rodon); Institut Gustave Roussy, Villejuif (P. Carde); Hôpital Laboché, Saint-Brieue (I. Yakoub); Hôpital de la Durance, Avignon (P. Souteyrand); Centre Hospitalier de la Cote Basque, Bayonnes (M. Renoux); Hôpital de Pontoise (J. Facquet-Danis); Hôtel-Dieu, Nantes (M. Hamidou); Hôpital René Huguenin, Saint-Cloud (F. Turpin); Hôpital d'Antibes (J-F. Dor); Hôpital Saint-Louis, Paris (J-P. Fermand); Hôpital Avicenne, Bobigny (N. Vigneron); Hôpital de Cimiez, Nice (A. Garnier); Hôpital de Saint-Germain en Laye (J.P. Le Loster). Statisticians: S. Chevret and C. Chasting, Departement de Statistiques et d'Informatique Médicale, Hôpital Saint Louis, Paris.

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