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Malignant Lymphomas

Long-term follow-up after fludarabine treatment in pretreated patients with chronic lymphocytic leukemia

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ABSTRACT

Background and Objectives. **A study update to assess long-term survival following fludarabine salvage treatment in previously treated patients with chronic lymphocytic lymphoma (CLL).**

Design and Methods. **From September 1992 to December 1995, 74 patients with advanced, relapsing B-cell CLL were enrolled in the study. Fludarabine was given for 5 consecutive days at the dose of 25 mg/m²/day in a 30 min infusion. Treatment was repeated every 28 days for a maximum of 6 courses.**

Results. **Nineteen (26%) patients achieved a complete response (CR) and 20 (27%) patients had a partial response (PR), giving an overall response rate of 53%. The median overall survival was 68 months, and there was a strong negative correlation with the number of previous treatments. The median time to progression was 18 months for patients who achieved a CR and 12 months for those with a PR.**

Interpretation and Conclusions. **The results obtained with fludarabine alone in this subset of CLL patients indicate the existence of a conspicuous disease-free survival period. This time window could be used to consolidate the initial response with either biological approaches or high-dose therapeutic strategies such as autologous bone marrow transplantation, with the aim of eventual eradication of the disease.**

Key words: fludarabine, CLL, pretreated, long-term follow-up

Conventional forms of treatment for chronic lymphocytic leukemia (CLL) are not curative and may be associated with substantial toxicities. Therefore, when to initiate therapy is an important issue. Chemotherapy drugs that are active in CLL include alkylating agents, such as chlorambucil and cyclophosphamide,[1-5] and corticosteroids.[6] As a matter of fact, the most frequently used combination chemotherapy regimens in CLL include chlorambucil plus prednisone and associations of cyclophosphamide, vincristine and prednisone.[7-9] Although no single-agent data are available for doxorubicin, this drug has been incorporated into combination regimens such as CHOP,[10] POACH,[11] and CAP.[12] No effective treatment for the management of patients who were resistant to these agents *de novo* or who developed resistance was available until the recent discovery of the activity of nucleoside analogs: fludarabine, 2-chlorodeoxyadenosine (2-CdA), and pentostatin. Of the three, fludarabine appears to be the most active in the treatment of CLL.[13-18] Objective response rates of 12% to 94% have been reported for fludarabine in previously treated CLL patients. Most of these patients were resistant to at least one other chemotherapeutic regimen but responded to treatment with fludarabine. Important correlations have been reported between response to fludarabine treatment and both stage of disease and extent of response to previous therapy in patients with CLL. Comparative studies have also shown that, among standard therapies, fludarabine is at least as effective, if not more, as CAP or CHOP in terms of response rate in patients with previously-treated, advanced CLL.[19]

Further long-term information is required on the role of fludarabine in pretreated CLL as regards the time to progression and overall survival. The aim of this report is to present an overall evaluation of the response to fludarabine alone in 74 pretreated patients with CLL.

Design and Methods

From September 1992 to December 1995, 74 patients with advanced, relapsing B-cell CLL were enrolled in the study. The inclusion criteria included being in stage III-IV disease according to the Rai classification[20] and having normal renal, pulmonary and hepatic functions. Approval was obtained from the Institutional Review Board. Informed consent was provided according to the Declaration of Helsinki and

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was obtained from all patients before the start of therapy. At the time of treatment with fludarabine we carried out a pretreatment evaluation including: medical history; physical examination; chest radiogram; ultrasonography to document tumor extension in the liver, spleen, and lymph nodes; complete blood cell counts; flow cytometry phenotyping; bone marrow aspiration and biopsy; direct Coombs' test. Fludarabine was given for 5 consecutive days at a dose of 25 mg/m^2/day in a 30 min infusion. Treatment was repeated every 28 days for a maximum of 6 courses. The patients were re-evaluated after every course of therapy and restaged after 3 and 6 courses, undergoing the same tests that had been performed in the pretreatment study. All patients received *Pneumocystis carinii* prophylaxis twice a week during the six months of treatment.

Patients' characteristics

The 74 patients comprised 55 males and 19 females ranging in age from 44 to 78 (median 62) years. Thirty-eight (51%) patients were in stage III and 36 (49%) in stage IV. All patients were previously treated and had relapsed following prior therapies; 24 (32%) patients had received 1 previous chemotherapeutic regimen, 32 (43%) patients had had 2 previous treatments, and the remaining 18 (25%) patients had been treated 3 or more times. The time from the initial diagnosis of CLL to the start of fludarabine therapy ranged from 27 to 65 months (median: 48 months). The patients' clinical characteristics at the time of fludarabine treatment are summarized in Table 1.

Response criteria

Response criteria were those previously recommended by the National Cancer Institute Working Group:[21] complete remission (CR) was defined as the disappearance of palpable masses, the recovery of satisfactory blood parameters (neutrophils to $\geq 1.5\times10^3$/µL, platelets to $\geq 100\times10^3$/µL, hemoglobin to ≥11 g/dL, lymphocytes $\leq 4\times10^3$/µL), and the clearance of bone marrow lymphocyte infiltration to below 30%. Partial remission (PR) was defined as a ≥50% decrease both in palpable masses and peripheral lymphocytosis, as well as recovery, or at least ≥ 50% improvement, of 1 or more of the abovementioned blood parameters. Patients with stable disease or progressive disease were considered as non-responders. Survival and time to progression curves were calculated according to the method of Kaplan and Meier.[22] Survival intervals were measured from diagnosis to death from any cause. Time to progression was measured from the first day of chemotherapy to the first detection of relapse from CR. Time to progression in PR patients was calculated at the occurrence of a ≥50% increase in size of residual abnormalities in liver, spleen, or lymph nodes, a consistently increased lymphocyte count to a level > 10^4/mL, or the development of anemia or thrombocytopenia.

Table 1. Clinical characteristics of 74 CLL patients.

No. of pts	74
Age (years):	
median	62
range	44-78
Sex	
M/F	55/14
Stage:	
III	38
IV	36
Previous treatments	
1	24
2	32
≥3	18

Table 2. Response rate of 74 patients with CLL.

	No. of pts	*CR (%)*	*PR (%)*	*ORR (%)*
Stage				
III	38	10 (26)	11 (29)	21 (55)
IV	36	9 (25)	9 (25)	18 (50)
Previous treatments				
1	24	10 (42)	8 (33)	18 (75)
2	28	7 (25)	8 (29)	15 (54)
3	22	2 (9)	4 (18)	6 (27)
Total	74	19 (26)	20 (27)	39 (53)

ORR= overall response rate

Results

Of the 74 patients who were evaluated for response, 19 (26%) achieved a CR, 20 (27%) had a PR, and the remaining 35 patients did not respond to therapy. The overall response rate was 53% and the overall median survival was 68 months. Response was rapid and became evident in all responding patients following no more than 3 courses of treatment. Response rates according to clinical stage and number of previous regimens are shown in Table 2. The overall survival curve is shown in Figure 1. Survival curves showed the existence of an inverse correlation with the number of previous treatments (p<0.0000) (Figure 2). The overall survival curves according to the disease stage (III vs IV) were not significantly different (not shown). The median times to progression for patients who achieved CR and PR were 18 (range: 6-42) and 12 (range: 6-34) months, respectively (Fig-

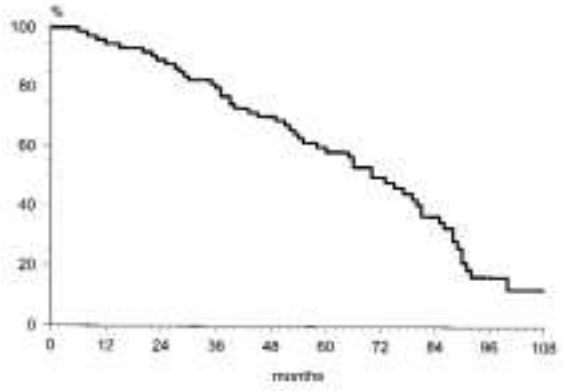

Figure 1. The overall survival curve of 74 CLL patients.

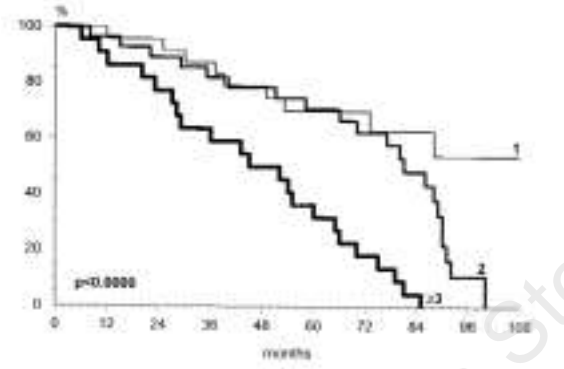

Figure 2. Survival curves with respect to number of previous treatments.

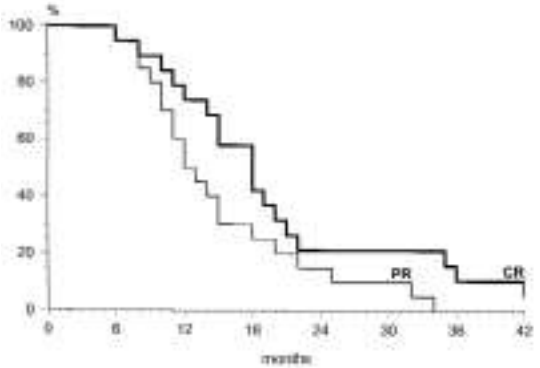

Figure 3. Time to progression according to final response to FLU.

ure 3). The CRs seemed to be more durable than PRs but no statistically significant difference was observable. No indication can be seen of a plateau developing on the curve of any group that might suggest the existence of a cured fraction. All but one of the patients who achieved CR or PR relapsed or progressed. This patient has now maintained CR for as long as 42 months; before the fludarabine treatment he was in stage III and had undergone one previous treatment with chlorambucil. The survival of responding patients (in CR and PR), after the development of progressive disease, correlated with the fludarabine-induced clinical response: 15/20 (75%) patients who had obtained PR died of disease progression, whereas only 2/19 (10.5%) of the CR patients died after relapsing.

A total of 52 patients have so far died: 39 due to progression of their disease or failure to respond to remission induction therapy, and 11 from infections, mostly in fludarabine-resistant patients. Regarding the other 2 patients, 1 died of pancreatic cancer and the other following the development of an aggressive non-Hodgkin's lymphoma (Richter's syndrome). Two isolated cases of autoimmune phenomena have been also recorded in this study: one patient developed autoimmune hemolytic anemia long after completion of fludarabine treatment, while another developed autoimmune thrombocytopenia during it. Both were well controlled by corticosteroids.

All infections were recorded between the third and the sixth cycle of therapy or within the first six months of follow-up. In detail, 4 of the 24 patients who had received fludarabine as first-line treatment developed infections, as well as 9 among the 32 and 10 of the 18 who had received it as second- and third-line treatment, respectively. Ten infections were minor and required only symptomatic treatment and/or oral antibiotics, while two were recorded as major and required parenteral antibiotics and/or hospitalization. Finally, eleven infections were fatal. All major and fatal infections involved either the respiratory tract or the sinuses. Of the eleven deaths due to infections, four were definitely attributed to staphylococcal septicemia, whereas the remaining seven were probably also of bacterial origin, although formal proof of this assumption could not be provided.

Discussion

Several studies,[10-17] including a previous evaluation by us,[5] have shown that even when fludarabine is used as a single agent in relapsed and/or refractory CLL patients it exerts significant therapeutic effects and can produce an overall response rate higher than 50%. The side

effects of this drug were acceptable, with febrile episodes and infections being the most frequent problems. As with all new drugs, in order to ascertain the real role of fludarabine, it is important to supplement this first wave of short-term data concerning overall response rate, CR rate and toxicity with long-term information such as time to progression and median overall survival. Few data of this sort have yet been reported with regard to the use of fludarabine in CLL. Only Keating and co-workers have so far updated their long-term results of fludarabine treatment in pretreated and untreated patients,[23,24] while Juliusson *et al.* have assessed the long-term survival obtained with another purine analog, 2-CdA, used alone as a salvage treatment agent for previously treated CLL patients.[25] In all these reports the maximum duration of follow-up reached by a fraction of patients was about 6-7 years.

With a median follow-up of 6.5 (range: 5-8) years and a time to progression of up to 42 months, the median duration of survival in our patients was as long as 68 months. Our study, exclusively involving relapsed patients in advanced stage, produced an overall response rate of 53%, with a CR rate of 26%. The number of prior treatments was inversely correlated with overall survival: the higher the former, the shorter the latter. The median time to progression was 12 months in PR patients and 18 months in CR patients, with no statistically significant difference. In terms of long-term continuous CR, only 1 patient has remained in relapse-free follow-up for as long as 42 months. Globally, 52/74 (70%) patients died during the period of study, with a minimum follow-up of 4 years. In particular the death rate was much greater in the PR subset with respect to the CR one (75% vs. 10.5%). Toxicity-wise, most infections recorded during and after fludarabine treatment occurred in patients who were refractory to the drug, while those who responded to it seemed to run a much lower risk of developing such complications.

These data with an extended long-term follow-up help further definition of the efficacy of fludarabine as a single agent in pretreated advanced CLL with respect to the chance of obtaining a long period of disease reduction or disease-free survival in more than half of the patients. This important time window of over 1 year could be utilized to consolidate the initial clinical response with further therapeutic approaches, such as autologous bone marrow transplantation for the CR patients,[26] and biological therapy such as the anti-CD20 monoclonal antibody[27] or Campath-1H[28] for those in PR. Our findings reinforce the role of fludarabine alone as an important therapeutic presidium in both front- and second-line strategies, with the ultimate aim of eradicating the disease after following a series of different sequential therapeutic steps.[29,30] With this high-profile goal in mind, the most recommendable first step seems to be fludarabine, most probably in combination with other drugs.[31,32]

Contributions and Acknowledgments

PLZ designed the study and wrote the paper. MB and DR helped PLZ with the data analysis interpretation. MM, PA, VS, and MT were involved in clinical assessment of the patients. ST critically revised the paper and gave the final approval for its submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- Fludarabine is a safe and efficacious drug in pretreated CLL patients.
- Even used alone, fludarabine is able to induce clinical remissions in more than half of such patients, conspicuously expanding the disease-free period for most of them.

References

1. Knospe WH, Loeb V Jr, Huguley CM Jr, et al. Proceedings: bi-weekly chlorambucil treatment of chronic lymphocytic leukemia. Cancer 1974; 33:555-62.
2. Han T, Ezdinli EZ, Shimaoka K, et al. Chlorambucil vs. combined chlorambucil-corticosteroid therapy in chronic lymphocytic leukemia. Cancer 1973; 31:502-8.
3. 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.
4. Keller JW, Knospe WH, Raney M, et al. Treatment of chronic lymphocytic leukemia using chlorambucil and prednisone with or without cycle-active consolidation chemotherapy. A southeastern Cancer Study Group Trial. Cancer 1986; 58:1185-92.
5. Rai KR. Chronic lymphocytic leukaemia. Current strategy and new perspectives of treatment. Haematologica 1999; 84(EHA4 Educational Book):94-5.
6. Ezdinli EZ, Stutzman L, Aungst CW, et al. Corticosteroid therapy for lymphomas and chronic lymphocytic leukemia. Cancer 1969; 23:900-9.
7. Liepman M, Votaw ML. The treatment of chronic lymphocytic leukemia with COP chemotherapy. Cancer 1978; 41:1664-9.
8. Oken MM, Kaplan ME. Combination chemotherapy with cyclophosphamide, vincristine, and prednisone in the treatment of refractory chronic lymphocytic leukemia. Cancer Treat Rep 1979; 63:441-7.

9. Montserrat E, Alcala A, Parody R, et al. Treatment of chronic lymphocytic leukemia in advanced stages: a randomized trial comparing chlorambucil plus prednisone versus cyclophosphamide, vincristine, and prednisone. Cancer 1985; 56:2369-75.
10. Long-term results of the CHOP regimen in stage C chronic lymphocytic leukaemia. French Cooperative Group on Chronic Lymphocytic Leukaemia. Br J Haematol 1989; 73:334-40.
11. Keating MJ, Scouros M, Murphy S, et al. Multiple agent chemotherapy (POACH) in previously treated and untreated patients with chronic lymphocytic leukemia. Leukemia 1988; 2:157-64.
12. Keating MJ, Murphy S, Hester J, et al. Long-term results of CAP therapy in chronic lymphocytic leukemia. Leuk Lymphoma 1991; 2:391-7.
13. Grever MR, Kopecky KY, Coltman CA, et al. Fludarabine monophosphate: a potentially useful agent in chronic lymphocytic leukemia. Nouv Rev Fr Hematol 1988; 30:457-9.
14. Keating MJ, Kantarjian H, Talpaz M, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. Blood 1989; 74:19-25.
15. 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.
16. De Rossi G, Mauro FR, Caruso R, Monarca B, Mandelli F. Fludarabine and prednisone in pretreated and refractory B-chronic lymphocytic leukemia (B-CLL) in advanced stages. Haematologica 1993; 78:167-71.
17. Zinzani PL, Lauria F, Rondelli D, et al. Fludarabine in patients with advanced and/or resistant B-chronic lymphocytic leukemia. Eur J Haematol 1993; 51:93-7.
18. Stelitano C, Morabito F, Kropp MG, et al. Fludarabine treatment in B-cell chronic lymphocytic leukemia: response, toxicity and survival analysis in 47 cases. Haematologica 1999; 84:317-23.
19. Johnson S, Smith AG, Loffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet 1996; 347:1432-8.
20. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975; 46: 219-34.
21. 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.
22. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. JAMA 1958; 53:457-81.
23. 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.
24. 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.
25. Juliusson G, Liliemark J. Long-term survival following cladribine (2-chlorodeoxyadenosine) therapy in previously treated patients with chronic lymphocytic leukemia. Ann Oncol 1996; 7:373-9.
26. Meloni G, Mauro FR, Proia A, Mandelli F. Chronic lymphocytic leukemia: from palliative therapy to curative intent. Haematologica. 1998; 83:660-2.
27. Winkler U, Jensen M, Manzke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (Rituximab, IDEC-C2B8). Blood 1999; 94:2217-24.
28. Osterborg A, Dyer MJ, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of Campath-1H Treatment in chronic lymphocytic leukemia. J Clin Oncol 1997; 15:1567-74.
29. Binet JL. Prognostic factors in chronic lymphocytic leukaemia. Haematologica 1999; 84(EHA4 Educational Book):96-7.
30. Catovsky D. Morphology, atypical chronic lymphocytic leukaemia and prognostic features affecting choice of therapy. Haematologica 1999; 84(EHA4 Educational Book):92-3.
31. Frewin R, Turner D, Tighe M, Davies S, Rule S, Johnson S. Combination therapy with fludarabine and cyclophosphamide as salvage treatment in lymphoproliferative disorders. Br J Haematol 1999; 104:612-3.
32. Zaja F, Rogato A, Russo D, Marin L, Silvestri F, Baccarani M. Combined therapy with fludarabine and cyclophosphamide in relapsed/resistant patients with B-cell chronic lymphocytic leukemia and non-Hodgkin's lymphomas. Eur J Haematol 1997; 59:327-8.