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.

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Key words: fludarabine, CLL, pretreated, long-term follow-up
was obtained from all patients before the start of therapy. At the time of therapy with flu-
darabine we carried out a pretreatment evaluation including: medical history; physical exami-
nation; 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. Flu-
darabine was given for 5 consecutive days at a
dose of 25 mg/m²/day in a 30 min infusion.
Treatment was repeated every 28 days for a max-
umum of 6 courses. The patients were re-evalu-
ated 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 fol-
lowing prior therapies; 24 (32%) patients had
received 1 previous chemotherapeutic regimen,
32 (43%) patients had had 2 previous treat-
ments, 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 fludara-
bine therapy ranged from 27 to 65 months
(median: 48 months). The patients’ clinical characteris-
tics at the time of fludarabine treatment are summarized in Table 1.

Response criteria
Response criteria were those previously rec-
ommended by the National Cancer Institute Working Group: a complete remission (CR) was defined as the disappearance of palpable masses, the recovery of satisfactory blood parameters (neutrophils to \( \geq 1.5 \times 10^9/\mu L \), platelets to
\( \geq 100 \times 10^9/\mu L \), hemoglobin to \( \geq 11 \ g/dL \), lymphocytes \( \leq 4 \times 10^9/\mu L \)), and the clearance of bone marrow lymphocyte infiltration to below 30%.
Partial remission (PR) was defined as a \( \geq 50\% \) decrease both in palpable masses and peripheral lymphocytosis, as well as recovery, or at least \( \geq 50\% \) improvement, of 1 or more of the above-
mentioned blood parameters. Patients with sta-
ble disease or progressive disease were consid-
ered as non-responders. Survival and time to
progression curves were calculated according to the method of Kaplan and Meier. Survival intervals were measured from diagnosis to death from any cause. Time to progression was mea-
sured from the first day of chemotherapy to the

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Table 1. Clinical characteristics of 74 CLL patients.

<table>
<thead>
<tr>
<th>No. of pts</th>
<th>74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): median</td>
<td>62</td>
</tr>
<tr>
<td>range</td>
<td>44-78</td>
</tr>
<tr>
<td>Sex</td>
<td>M/F</td>
</tr>
<tr>
<td></td>
<td>55/14</td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>38</td>
</tr>
<tr>
<td>IV</td>
<td>36</td>
</tr>
<tr>
<td>Previous treatments</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>18</td>
</tr>
</tbody>
</table>

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Table 2. Response rate of 74 patients with CLL.

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

ORR= overall response rate

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first detection of relapse from CR. Time to pro-
gression in PR patients was calculated at the occurrence of a \( \geq 50\% \) increase in size of residual abnormalities in liver, spleen, or lymph nodes, or an increase in lymphocyte count to a level \( > 10^4/mL \), or the development of anemia or thrombocytopenia.

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 sur-
vival 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-
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, including a previous evaluation by us, 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 Julliusson 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 6.6 (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 28%. 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 antibody27 or Campath-1H28 for those in logical therapy such as the anti-CD20 monotherapy and Campath-1H29 combination with further 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

### 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


