Fludarabine: A New Agent With Major Activity Against Chronic Lymphocytic Leukemia


Fludarabine was used to treat 68 patients with previously treated chronic lymphocytic leukemia (CLL). Nine (13%) patients achieved a complete remission and 30 (44%) a partial remission. The response rates for Rai stages 0 to 2, 3, and 4 were 64%, 58%, and 50% respectively. Seventeen (43%) of the 40 Rai stage 1 to 3 patients and four (19%) of the Rai stage 4 patients returned to Rai stage 0. Survival was strongly correlated with the final Rai stage achieved. The survival of the 11 partial responders with residual disease consisting only of residual bone-marrow nodules was similar to the complete responders (36 months) and superior to the other partial response patients (16 months). The response to fludarabine was rapid, with 36 (92%) of the 39 responders having achieved at least a partial response following the first three courses. Complete responses occurred in the blood, liver, spleen, and lymph nodes in 48% to 69% of the patients. Eradication of all disease in the bone marrow occurred in only 13% of the cases. Neutropenia and thrombocytopenia occurred in 56% and 25% of evaluable courses. Major infections occurred in 9% of evaluable courses and fevers of unknown origin or minor infections in 12% of courses respectively. Myelosuppression and infection were more common in patients with initial Rai stages 3 and 4 and in nonresponding patients. Other toxicity was mild. No CNS toxicity was noted.

We have previously reported the preliminary results of this study in abstract form.19

Herein, we summarize our experience with fludarabine in 68 previously treated patients with CLL. The association of prognostic factors with response and survival is analyzed.

PATIENTS AND METHODS

Sixty-eight patients with CLL were entered on this Phase I-II study between March 1985 and December 1987. The median age was 60 years, with a range of 32 to 79 years. Fifty (74%) were male. The median pretreatment WBC count was 71,000/μL. The median marrow cellularity was 80%, and median percentage of marrow lymphocytes was 90%. The time from initial diagnosis of CLL to the start of fludarabine ranged from 5 to 220 months (median 64 months). The time from initial treatment of the CLL to the start of fludarabine varied from 2 months to 8 years (median of 45 months). Sixty-three patients had received prior cytotoxic chemotherapy for CLL. The other five patients had been treated for diffuse, small lymphocytic lymphoma (Table 1) that had developed a leukemic phase (~4,000 monoclonal lymphocytes per μL). Fifty-nine patients had received prior alkylating agents (chlorambucil only in 12 patients, cyclophosphamide only in 18 patients, and both agents in 29 patients). Other agents that had been given included corticosteroids (59 patients), vincristine (44 patients), doxorubicin (29 patients), cytosine arabinoside (24 patients), cisplatin (11 patients), and human or recombinant alpha-interferon (five patients). No significant difference in initial characteristics was demonstrated.

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the United States. With rare exceptions, CLL presents as a monomorphic accumulation of small B-cell lymphocytes involving the blood, bone marrow, lymph nodes, liver, and spleen. The phenotype of the cells is characterized by expression of surface membrane immunoglobulin, CD5 surface antigen, and a marked preponderance of either kappa or lambda light chains. The natural history is diverse, as patients with evidence of bone marrow failure such as anemia or thrombocytopenia have a median survival of 2 years; and those with lymphocytosis only have a median survival of more than 10 years.

Most regimens used in the treatment of CLL are based on the activity of alkylating agents and corticosteroids against this disease. Chlorambucil and steroids in combinations have become the standard initial therapy, resulting in complete or partial remission (CR or PR) in 40% to 77% of previously treated patients, yielding CR and PR rates on the order of 30% and median survivals of approximately 15 months.2,3,9,10

Fludarabine (9-β-d-arabinofuranosyl-2-fluoro-adenine monophosphate) is a fluorinated analogue of adenine that is relatively resistant to deamination by adenosine deaminase.11 Although severe demyelination was noted when high doses were used for acute leukemia,12-14 this was not observed when lower doses were used to treat solid tumors and lymphoma.15,16 The major dose-limiting toxic effect noted in the latter studies was myelosuppression, most commonly, leukopenia. Fludarabine causes lymphopenia, depleting normal T lymphocytes more markedly than B lymphocytes.17 However, eight of 25 patients with lymphoma (presumably B-cell tumors) responded to fludarabine.18 Grever et al18 were the first to report encouraging results using fludarabine to treat CLL. Nine (35%) of 26 patients in that study responded.18

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assigned a Rai and Binet stage at the time of initiation of fludara- 
ery lymphocytosis with a cell count greater than 10,000/μL on at 
egent.
quantitation of their immunoglobulin levels prior to receiving 
sample aspiration. Fifty-two patients underwent a bone marrow 
white cell and platelet counts; a chemical survey; and bone marrow 
spleen, and lymph nodes; complete blood cell counts; differential 
physical examination to document tumor measurements in the liver, 
binet," Pretreatment evaluation included a medical history and 
lymphocytes in the bone marrow. Each patient’s disease was 
least two previous occasions 1 month apart and had 30% or more 
patients, (This was not mandatory in the Phase I portion of the study). 
biopsy within 1 month preceding 
ons of fludarabine therapy.
Forty-nine patients had surface marker analysis performed within 1 
progressive disease. Response of disease that had been detected only on 
radiologic examination was not considered in the evaluation of 
clinical response. The criteria for CR and PR at each site are shown 
Table 2. Complete responders had to achieve CR status in all 
involved sites, while partial responders achieved at least a PR in all 
involved sites.
A subset of patients was identified within the PR category and 
were classified as nodular PR. In these patients the only evidence of 
disease was persistence of lymphoid nodules in the bone marrow, 
without evidence of a diffuse or infiltrative pattern. Apart from this, 
these patients fulfilled the criteria for CR. The number of residual 
nodules was not considered varying from one to multiple. No studies 
were performed to identify the clonality of the nodules. Patients were 
considered to have resistant disease if they had achieved less than PR 
criteria after at least three courses or had progressive disease (>25% 
increase in nodes, liver, spleen size, or white cell count) at any stage 
of treatment. Approval was obtained from the Institutional Review 
Board for these studies. Patients (and/or volunteers) were informed 
that blood (and/or bone marrow or tissue) samples were obtained for 
research purposes and that their privacy would be protected.

RESULTS
Response and survival. Thirty-nine patients (57%) 
achieved either a CR or a PR. Nine patients (13%) achieved 
a CR, 11 (16%) a nodular PR, and 19 (28%) a PR. Of the 29 
patients who failed to achieve a response, 19 were taken off 
study because of refractory disease, while ten died during the 
study (seven during the first three courses of therapy and 
three during later courses). Overall 36 of 68 patients have 
died. The median survival overall was 16 months. While all 
but one of the 20 patients who achieved CR or nodular PR 
are still alive (4 to 37 months), seven of those who achieved 
PR have subsequently died. The nodular PR patient died 
secondary to treatment of acute myelogenous leukemia that 
developed while she was still in remission from CLL. This 
patient had previously achieved a CR from a myelodysplastic 
syndrome diagnosed synchronously with the CLL. Of the

Table 2. Criteria for Response in CLL

<table>
<thead>
<tr>
<th>Response</th>
<th>Blood</th>
<th>Marrow</th>
<th>Liver/Spleen</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>&lt;4,000 lymphocytes/μL</td>
<td>&lt;30% lymphocytes, no nodules*</td>
<td>Impalpable</td>
<td>No pathologic nodes</td>
</tr>
<tr>
<td>PR</td>
<td>&gt;4,000 lymphocytes/μL and &gt;1 log reduction</td>
<td>≥50% decrease in infiltrate† with ≥30% lymphocytes or nodules</td>
<td>≥50% decrease in span below low coastal margin</td>
<td>≥50% decrease in product of perpendicular diameters</td>
</tr>
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</table>

* Nodular PR if CR by all criteria except for persistence of lymphoid nodules.
† Infiltrate = % lymphocytes × marrow cellularity.
The survival of these two groups combined was significantly different from that of the PR patients or nonresponders (patients dying in the first course excluded; Fig 1). The survival times of the two Rai stage 0 patients were 51+ and 86+ weeks. Although no significant difference in survival is noted between the 23 Rai stage I-II and the 43 Rai stage III-IV patients, the earlier stage patients had a somewhat better prognosis (Fig 2).

Nineteen of the nonresponding patients were taken off the study because of resistant disease. Thirteen patients received subsequent therapy, with only one achieving a minor response. After discontinuation of fludarabine, the median survival of the 19 resistant patients was 9 weeks.

Response to treatment was rapid. Thirty-six patients achieved a response after three courses of therapy (CR, four patients; nodular PR, six patients; PR, 26 patients). One of the six patients who achieved a nodular PR after three courses achieved a CR with continued treatment, whereas of the 26 patients who were in PR after three courses, 4 (15%) obtained a CR and 5 (19%) a nodular PR with continued treatment. Of the 14 patients who achieved less than a PR after three courses and who continued on treatment, none achieved a CR, one (7%) achieved a nodular PR, and two (14%) obtained a PR.

The response rate for the patients who had not previously received an alkylating agent was 5/9 (56%). Two of five patients with a previous period of diffuse well-differentiated lymphoma responded. No difference in response rate was noted for the two dose levels of 25 and 30 mg/m²/d (10/19, 53% v 29/49, 59%). Five (25%) of 20 patients with a CR or nodular PR have had a recurrence of disease compared with seven (37%) of the 19 patients with a PR. Recurrent disease was defined as a 50% or greater increase in absolute lymphocyte count to at least 10,000/μL; marrow lymphoid infiltrate; or clinically palpable disease in liver, spleen or lymph nodes. The median time to disease progression was 13
months for the PR patients compared with 21 months for the CR or nodular PR patients. The median follow-up time was 15 months (range 4 to 37 months).

**Prognostic factors for response and survival.** The CR and PR rates according to involved site of the disease were comparable, although the CR rate in bone marrow was lower than were CR rates at other sites. The respective CR and PR percentages at the various sites were as follows: blood, 69% and 8% in 64 evaluable patients; bone marrow, 13% and 44% in 52 patients; liver, 52% and 22% in 23 patients; spleen, 55% and 16% in 31 patients; and nodes, 48% and 29% in 52 patients.

No prognostic factor was significantly associated with response at the P < .05 level, although a trend was noted for earlier Rai and Binet stages, lower WBC count, fewer lymph-node sites, higher hemoglobin level, higher platelet counts, higher serum albumin levels, and lower serum alkaline-phosphatase levels to be associated with higher response rates (Table 3). Similarly, the only factors significantly associated with survival were the serum albumin and alkaline phosphatase levels and the platelet count (P < .01). The hemoglobin level and Rai and Binet stages were all moderately associated with survival (P < .05 to .10). The number of prior treatment attempts and the time from initial treatment to the start of fludarabine therapy were not significantly associated with response or survival.

The ability of treatment to improve the Rai stage was assessed in 62 patients whose eventual Rai stage of disease was evaluable. Improvement in Rai stage was most likely to occur in patients with earlier stage disease (Table 4). The final Rai stage was strongly predictive of survival (P < .01), with the median survival time for the final Rai stage 0 being, 71+ weeks; I, 38+ weeks; II, 70 weeks; III, 37 weeks; and IV, 21 weeks.

**Toxicity.** The major toxicity associated with fludarabine treatment was infection. The most common febrile episodes were due to pneumonia (25 episodes) or to fever of unknown origin (FUO, 28 episodes). FUO was defined as having fever with no microbiological cause or clinical focus being identified. These episodes usually subsided in five to ten days. Septicemia alone occurred in four patients. The minor infections involved the oropharynx (six patients), sinuses (two patients), urinary tract (four patients), and soft tissues (four patients). The incidence of major infections (3/143 courses) was significantly (P < .01) lower in the patients who achieved CR or nodular PR than it was in either the PR or nonresponding patients (Table 5). The incidence of all febrile episodes and major infections decreased significantly in later courses of therapy (Table 5). Disseminated herpes zoster infections did not occur, although five patients had the infection in a dermatome distribution. No correlation was found between the initial IgG, IgA, and IgM levels, and infectious complications in the 33 patients for whom data were available.

Myelosuppression was common during treatment. Myelosuppression was not cumulative, as the incidence of neutropenia and thrombocytopenia was lower in courses 4 through 6 than in courses 1 through 3. Myelosuppression appeared more strongly related to the patient’s response to therapy than to the initial Rai stage of disease. Among patients stratified according to initial Rai stage, the incidence of neutropenia and thrombocytopenia was significantly lower in the CR and nodular PR group than in the PR and nonresistant.

<table>
<thead>
<tr>
<th>Table 4. Comparison of Initial Rai Stage With Final Stage</th>
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<tbody>
<tr>
<td>Initial Rai Stage</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>Overall</td>
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<tr>
<th>Table 5. Relationship Between Incidence of Febrile Episodes and Course Number and Response Category</th>
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<tr>
<td>Incidence (%)</td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Course No.</strong></td>
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<tr>
<td>1-3</td>
</tr>
<tr>
<td>4-6</td>
</tr>
<tr>
<td>&gt;6</td>
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<tr>
<td><strong>Best response</strong></td>
</tr>
<tr>
<td>CR + Nodular</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>Resistant</td>
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FLUDARABINE IN REFRACTORY CLL

Table 6. Association of Neutropenia (<500/µL) and Thrombocytopenia (<50,000/µL) With Initial Rai Stage and Response to Treatment

<table>
<thead>
<tr>
<th>Initial Rai Stage</th>
<th>Neutropenia Episodes/Evaluable Courses (%)</th>
<th>Thrombocytopenia Episodes/Evaluable Courses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR + Nodular PR</td>
<td>PR + Resistant</td>
</tr>
<tr>
<td>0-2</td>
<td>2/37(5)</td>
<td>23/40(58)</td>
</tr>
<tr>
<td>3-4</td>
<td>9/25(36)</td>
<td>66/76(87)</td>
</tr>
<tr>
<td>Total</td>
<td>11/62(18)</td>
<td>89/116(56)</td>
</tr>
</tbody>
</table>

sponder group. The exception to this was patients with Rai stages 0, 1, or 2 who had a low incidence of thrombocytopenia regardless of response status (Table 6). Neutropenia and thrombocytopenia were less common during later courses in patients who were responding, but this was not the case in the PR or nonresponding patients.

No other toxic effect was prominent. Nausea was uncommon (nine [2.7%] of 337 courses) as was stomatitis (1.5%) and diarrhea (1.8%). Alopecia did not occur. Neurologic symptoms also were uncommon. Three patients had symptoms of peripheral neuropathy: one had proximal muscle weakness, one had general muscle weakness, and one had paresthesiae. An additional patient complained of decreased hearing. No patient developed CNS symptoms, visual disturbance, or spinal tract symptoms or signs. Fatigue was reported during 3.6% of treatment courses and weight loss during 1.8% of courses.

DISCUSSION

This study demonstrates that treatment with fludarabine is associated with a major cytoreductive response in more than half of previously treated patients with CLL. The response is rapid and the tolerance excellent, with little toxicity except for that associated with infection. Comparison of results of fludarabine therapy with those of other regimens is difficult for several reasons. The criteria for response to treatment and for entry into studies involving CLL have often not been well defined. In addition, quantitation of the degree of prior therapy is difficult because of less well-defined criteria for discontinuing and subsequently reinitiating treatment. Lastly, most regimens used in previously treated patients are based largely on alkylating agents, which are usually the drugs used in the initial treatment of CLL.

Regimens such as CVP (cyclophosphamide, vincristine, and prednisone),24 the M2 regimen,2 or chlorambucil-steroid regimens2 have obtained PR rates of approximately 30% in previously treated patients. The POACH regimen (cyclophosphamide, vincristine, Adriamycin, prednisone, and cytosine arabinoside) yielded a response rate of 26% in 31 patients using the same entry and response criteria used in this study.2 The patient characteristics such as age, time from diagnosis to treatment, tumor burden, and Rai and Binet disease stages were comparable in this study and the POACH study. Response rates with fludarabine were superior to those with POACH for patients in all prognostic categories analyzed. The response to fludarabine was not strongly associated with the number of prior treatments the patients had received or with the duration of prior treatment. This may relate to the difficulty in establishing whether the patients were truly refractory to previous regimens.

The median survival in our study (16 months) was only slightly better than survivals reported in other series using POACH,2 CVP,24 or chlorambucil-prednisone therapy.3 As survival is strongly associated with response to treatment, the median survival would not be expected to improve when almost half the patients achieved less than a partial response. The CR rate for previously treated patients in this study, although modest (13%), was higher than those in other studies, where CRs were rare.1,7 Furthermore, some of those studies would consider the nodular PR patients in our study to be complete responders. The favorable survival and delayed disease recurrence in patients who achieved a CR or a nodular PR suggest that these patients will have a substantial survival with longer follow-up.

The subcategory of nodular PR patients fulfills the criteria for CR (including fewer than 30% lymphocytes in the bone marrow) apart from residual lymphoid nodules in the marrow. The other PR patients usually had a diffuse or infiltrative pattern in the marrow after treatment. The survival, tolerance of treatment, return to Rai stage 0, and duration of response in the nodular PR category all more closely resembled the CR category than the PR category. Thus the marrow pattern is significantly associated with prognosis, as has been described in untreated patients prior to treatment.22 As in other studies, improvement in the patients' clinical stage was strongly associated with survival.18,23

In this study the incidence of myelosuppression, morbidity, and mortality was associated not only with pretreatment stage but also more strongly with response to treatment. Most patients who achieved a CR or a nodular PR had excellent tolerance of the treatment and minimal myelosuppression, whereas those who achieved only a PR or who did not respond to treatment had significantly more myelosuppression as well as morbidity and mortality resulting from infection. These observations suggest that for unknown reasons a major cause of morbidity during treatment of patients with CLL who have been previously treated is the activity of the disease.20,21 Five (16%) of 31 patients treated with the POACH regimen died during the first course. Close clinical observation of patients with advanced-stage disease who receive fludarabine is essential, especially if the response to treatment has been modest. The customary approach to myelosuppression and infectious morbidity during treatment of CLL is to decrease the dosage of the agent(s). An alternative approach is to pursue achievement of a CR or a nodular PR with the same level of supportive care and surveillance that is given to acute leukemia patients, as response is so strongly associated with survival.

The acute tolerance to fludarabine was excellent; the drug had a high level of patient acceptance. The spectrum of
infections seen during treatment was typical of CLL cases, with a high incidence of sinopulmonary involvement. Herpes zoster was also relatively common. The infectious morbidity was more noticeable in early than in late courses and was less common in responding patients. No correlation was found between pretreatment immunoglobulin levels and infectious morbidity.

Severe neurotoxicity, as has been reported in studies of fludarabine given in higher doses to patients with acute leukemia, was not noted in this study. Four patients had symptoms suggestive of peripheral sensorimotor neuropathy; this was a much lower incidence than would have been anticipated with agents such as vincristine or cisplatin.

No prognostic factors emerged that could accurately identify patients who were likely to respond to fludarabine, although trends toward refractory disease were noted in patients with advanced tumor burden or marked marrow failure. The mechanism of action of fludarabine against CLL is uncertain, although it is thought to be related to the drug’s interference with adenosine nucleotide metabolism. Although normal T lymphocytes are more susceptible to fludarabine than are B lymphocytes, neither of the two study patients with T-cell CLL had any cytoreductive response to treatment.

The results achieved with fludarabine in previously treated patients are certainly superior to those of other single agents used against CLL. The response rates are comparable with many reported results using combination regimens in previously untreated patients. The cytoreductive efficacy and excellent tolerance to this drug in previously treated patients recommend its use in untreated patients. Studies of the mechanism of action of fludarabine could suggest more appropriate schedules to optimize the therapeutic index and thus to allow the development of this new agent to its greatest potential.

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MJ Keating, H Kantarjian, M Talpaz, J Redman, C Koller, B Barlogie, W Velasquez, W Plunkett, EJ Freireich and KB McCredie