Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia

By Susan M. O’Brien, Hagop M. Kantarjian, Jorge Cortes, Miloslav Beran, Charles A. Koller, Francis J. Giles, Susan Lerner, and Michael Keating

Purpose: To assess the efficacy of combination therapy with fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia (CLL) based on data suggesting in vitro synergistic activity of the two agents.

Patients and Methods: A total of 128 patients with CLL were treated with fludarabine 30 mg/m² intravenously daily for 3 days and cyclophosphamide at either 500 mg/m² daily for 3 days (n = 11), 350 mg/m²/d for 3 days (n = 26), or 300 mg/m² daily for 3 days (n = 91). The cyclophosphamide dose was decreased because of myelosuppression in the early part of the study. Patients were divided into four groups based on the expectation for response to single-agent fludarabine, including previously untreated patients, patients previously treated with alkylating agents, patients successfully treated with alkylating agents and fludarabine but relapsing, and patients refractory to fludarabine with or without alkylating agents.

Results: Fludarabine and cyclophosphamide produced > 80% response rates in all patients not refractory to fludarabine at the start of therapy as well as a 38% response rate in patients who were refractory to fludarabine. The complete remission (CR) rate was 35% in previously untreated patients, which was not significantly different from the CR rate in historical control patients treated with single-agent fludarabine. However, residual disease assessed by flow cytometry occurred in only 8% of previously untreated patients achieving CR, and median time to progression has not been reached after a median follow-up of 41 months. The main complication of therapy was related to myelosuppression and infection. Neutropenia to less than 500 x 10⁹/L was noted in 48% of patients who received cyclophosphamide 300 mg/m². Pneumonia or sepsis occurred in 25% of patients, and fever of unknown origin occurred in another 25%. Pneumonia or sepsis were significantly more frequent in patients who were refractory to fludarabine at the start of combination chemotherapy.

Conclusion: Fludarabine and cyclophosphamide seem to have a significant advantage over single-agent fludarabine in the salvage setting. Although the CR rate was not increased in previously untreated patients, residual disease detected by flow cytometry was rare and remission durations seemed to be prolonged in this subset. Myelosuppression and infection remain the most significant complications of therapy in CLL.


FLUDARABINE IS the most active single agent in the treatment of chronic lymphocytic leukemia (CLL).1,2 Response rates of 45% to 65% are reported with fludarabine salvage therapy in CLL; up to 80% of previously untreated patients respond to fludarabine.1,8 Nevertheless, complete remissions are uncommon, and even among patients who meet the standard criteria for complete remission, residual disease can often be detected. Thus, although remissions can be long lasting, all patients inevitably relapse. More effective treatments in CLL are needed, with the long-term goal of cure. Fludarabine is an attractive agent for use in combination chemotherapy since it has little extramedullary toxicity; major side effects are related to myelosuppression and immunosuppression. Alkylating agents are also active against CLL. Before the discovery of fludarabine, chlorambucil was the mainstay of treatment for CLL.

Cyclophosphamide (CTX), another effective alkylating agent in CLL, was chosen for combination with fludarabine because most previously treated patients would have had exposure to and/or be resistant to chlorambucil, and preclinical studies suggested added or synergistic activity of these two agents.9,10 DNA interstrand crosslinks induced in CLL lymphocytes after in vitro exposure to activated cyclophosphamide (4-HC) were rapidly repaired and could not be detected after 6 to 8 hours of incubation. However, when CLL cells were exposed to small doses of fludarabine with 4-HC incubation, 80% of DNA cross-links were still detectable 24 hours later.9 Presumably, this was a result of inhibition of DNA repair enzymes by fludarabine, which allowed these cross-links to persist, thus potentially increasing cell-kill. Another study showed synergistic cytotoxic activity against CLL cells in vitro with the combination of...
fludarabine and mafosfamide. Mafosfamide also increased apoptosis induced by fludarabine.

In this study, we report our results with fludarabine and CTX combination therapy in CLL, and compare outcome with that from single-agent fludarabine therapy.

PATIENTS AND METHODS

Study Group

Between 1995 and 1998, 128 patients with CLL requiring therapy were entered onto the study, after informed consent was obtained according to institutional guidelines. All patients had a pretreatment evaluation, including history and physical examination, complete blood counts, differential and platelet counts, liver and renal function studies, bone marrow aspiration and biopsy, and marrow samples for immunophenotyping. Entry criteria required (a) a confirmation of the diagnosis with a monotypic expansion of lymphoid cells $\geq 10 \times 10^9$/L, morphologically consistent with CLL (small lymphocytes), (b) more than 30% lymphocytes in the bone marrow, and (c) normal renal (creatinine $< 2.0$ mg/100 mL) and hepatic (bilirubin $< 2.0$ mg/100 mL) functions. Patients with Rai stages III and IV disease were eligible. Patients with stages 0 to II were eligible if they had evidence of active disease as indicated by an increase in symptoms related to leukemia, including weight loss $\geq 10\%$ over a 6-month period, temperature of 38°C without evidence of infection, extreme fatigue, massive or progressive hepatosplenomegaly, or massive or progressive lymphadenopathy.

Therapy

Patients received fludarabine 30 mg/m² intravenously over 30 minutes daily for 3 days. The initial 11 patients received CTX 500 mg/m² over 1 hour daily for 3 days. Because of significant myelosuppression, the subsequent 26 patients received CTX 350 mg/m² for 3 days. This was well tolerated in the initial courses, but cumulative myelosuppression became a problem. When this was recognized, the last 91 patients received CTX 300 mg/m² for 3 days. Courses were repeated every 4 to 6 weeks, depending on recovery of counts, with courses being delayed until the platelet count was more than 80 $\times 10^9$/L and the WBC count was more than 2 $\times 10^9$/L. In patients beginning therapy with thrombocytopenia, courses were held only if the platelet count had not returned to baseline by 4 weeks. Subsequent courses were dose reduced for lack of recovery of blood counts to the aforementioned levels by 5 weeks or for pneumonia, septicemia, or life-threatening infection; in such cases, CTX was reduced by one dose level (500 to 350, 350 to 300, and 300 to 250 mg/m² daily for 3 days), depending on the starting dose of CTX. Six courses of therapy were planned. Prophylactic antibiotics and/or growth factors were not used routinely. However, prophylaxis with trimethoprim-sulfa twice weekly was recommended for patients who required corticosteroids for any reason, usually because of autoimmune phenomena. Therapeutic antibiotics and growth factor support could be used at the discretion of the treating physician.

Response Criteria

Response criteria were those previously defined by the National Cancer Institute (NCI) Working Group. Complete remission (CR) required the disappearance of all palpable disease, normalization of the blood counts (neutrophils $> 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L, hemoglobin $> 11$ g/dL), bone marrow aspirate lymphocyte percentage $< 30\%$, and no evidence of disease on bone marrow biopsy. A nodular partial remission (PR-nodular) required the same criteria as for CR with the exception that lymphoid nodules could be seen on bone marrow biopsy. A partial remission (PR) required 50% or more reduction in palpable disease as well as one or more of the remaining features: neutrophils $\geq 1.5 \times 10^9$/L or 50% improvement over baseline, platelets more than 100 $\times 10^9$/L or 50% improvement over baseline, and hemoglobin more than 11.0 g/dL or 50% improvement over baseline without transfusions. No bone marrow evaluation was required for determination of PR. Computerized tomography scans were not required to evaluate response. After completion of therapy, patients were reevaluated at 3-month intervals with history, physical examination, and blood counts. Bone marrow examination was performed every 6 months.

Statistical Considerations

Associations between patient characteristics and response outcome were evaluated by $\chi^2$ test. Cutpoints for quantitative variables were those defining abnormal levels or others commonly used. Distributions of survival and time to progression were estimated by the method of Kaplan and Meier. Survival intervals were measured from first day of chemotherapy until death; deaths from all causes were included. Time to progression was measured from the start of chemotherapy until detection of relapse.

Sample Size Determination

Previously untreated patients. The response rate to fludarabine in previously untreated patients is 80%. However, the CR rate is only 33%. The objective of this study was to increase the historical control of 33% CR rate to $\geq 55\%$. Fourteen patients were to be entered onto the first stage and the study terminated if the response rate was less than 33% (five of 14 patients). Otherwise, 22 additional patients, for a total of 36, were entered. Therapy would not be recommended for further study at the end of the second stage if the response rate was less than 42% (15 of 36). This design assumes type I and II error rates of 10% and has an average sample size of 25 patients and a 49% probability of early termination if the true response rate is 33%.

Patients previously treated with alkylating agents. The objective of the study was to recommend further investigation of the combination if the true response rate was $\geq 60\%$ and to reject the regimen for further trials if the true response rate was $\leq 45\%$ (type I and II errors $= 0.10$). Results were to be analyzed after the first 32 patients and the trial terminated if 14 or fewer responses were observed. Otherwise, an additional 46 patients could be entered, for a total of 78 patients. If a total of 40 or fewer responses were observed, the regimen would not be recommended for further clinical investigations. Using these guidelines, the expected sample size is 54 patients if the true response rate of the combination regimen is 45%.

Although a total of 78 such patients could be entered, only 20 were accrued because of a marked decline in the referral of pretreated patients who had not received prior fludarabine to M.D. Anderson Cancer Center.

Patients previously treated with alkylating agents and fludarabine. Twenty-two patients could be entered onto the first stage and the study terminated if the response rate was less than 31.8% (seven of 22). Otherwise, 24 additional patients, for a total of 46, could be entered. Therapy would not be recommended for further study at the end of the second stage if the response rate was less than 37% (17 of 46). This design assumes type I and II error rates of 10% and has an average
sample size of 30 patients and a 67% probability of early termination if the true response rate is 30%.

Patients failing alkylating agents and fludarabine. The study would be stopped for lack of response if zero of 14 responses were observed or fewer than two responses were observed among the first 25 patients. This rule provides a 0.03 probability of early stopping if the true response rate is 0.2, and 0.64 and 0.97 probabilities of early stopping if the true response rates are 0.05 and 0.01, respectively.

RESULTS

Patient Characteristics

Patients were divided into four groups with different expectations for response to single-agent fludarabine: (1) previously untreated patients receiving fludarabine and CTX as initial therapy; (2) patients previously treated with alkylating agents either alone or in combination; these patients had not received therapy with nucleoside analogs; and (3) patients who had received therapy with alkylating agents and fludarabine and had initially responded to fludarabine therapy but then relapsed. The final group (4) included patients who had failed alkylating agents and fludarabine-based therapy previously. This meant that patients had relapsed after or were refractory to alkylating agents and had failed to achieve at least a PR with their last fludarabine-based therapy. Sixty-two percent of the fludarabine-refractory patients were also refractory to alkylating agents (ie, had progressed on therapy), and the remaining 38% had responded to alkylating agents but then relapsed (but failed therapy with fludarabine). Expectations for response to single-agent fludarabine in the four groups were 70% to 80%, 50% to 60%, 30% to 35%, and less than 5%, respectively.

Patient characteristics are detailed in Table 1. The median age was 58 years (range, 29 to 92 years). Forty-seven percent of patients had Rai stage III to IV disease. Thirty-four patients (27%) were previously untreated. Among previously treated patients, the median number of prior regimens was two (range, one to seven); 38% of previously treated patients had disease refractory to alkylating agents, and 31% had failed prior fludarabine therapy.

Response

Response rates to fludarabine and CTX detailed by the prior therapy are listed in Table 2. Patients not refractory to fludarabine and/or alkylating agents at the time of entry onto the study had an overall response rate of 80% or greater. Interestingly, patients refractory to fludarabine with or without alkylating agents had a response rate of 38%, which suggests that the combination may be synergistic in this group. CRs, defined using the revised NCI Working Group criteria,11 which require complete normalization of bone marrow biopsy, ranged from 3% in fludarabine-refractory patients to 35% in previously untreated patients. The median number of courses administered to all patients was three (four in responders and three in nonresponders).

There was no significant difference in overall response rates according to CTX dose. However, given the high overall response rate in nonfludarabine-refractory patients and the smaller number of patients treated at the 350-mg/m² dose level, the ability to detect such a difference was limited. The CR rate in previously untreated patients treated with CTX 300 mg/m² was 39%, compared with 38% at the 350-mg/m² dose. (Two previously untreated patients received CTX 500 mg/m² and both achieved PR). The CR rate in previously treated patients (not refractory to fludarabine at the start of therapy) was 11% with CTX 300 mg/m² and 14% with CTX 350 mg/m².

Side Effects

Prophylactic ondansetron was administered to all patients. Still, 40% of patients had nausea and vomiting that was usually mild but required further therapy with oral agents. Nausea with or without vomiting did not begin until day 3, and it persisted for another 1 to 2 days. Other extramedullary toxicities were minor (Table 3).

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics (N = 128)</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
</tr>
<tr>
<td>Prior regimens</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2-3</td>
</tr>
<tr>
<td>≥ 4</td>
</tr>
<tr>
<td>Refractory</td>
</tr>
<tr>
<td>Alkylating agents</td>
</tr>
<tr>
<td>Fludarabine</td>
</tr>
<tr>
<td>β₂ microglobulin</td>
</tr>
<tr>
<td>&gt; 3.0 mg/L</td>
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<td>&gt; 4.0 mg/L</td>
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*Percentage of previously treated patients.

<table>
<thead>
<tr>
<th>Table 2. Response to Fludarabine and Cyclophosphamide by Prior Therapy</th>
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<td>Prior Therapy</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Alkylating agents</td>
</tr>
<tr>
<td>Alkylating agent + fludarabine*</td>
</tr>
<tr>
<td>Alkylating agent + fludarabine†</td>
</tr>
</tbody>
</table>

*Sensitive to last treatment.
†Refractory to last treatment.
Significant side effects with fludarabine and CTX included myelosuppression and infections. Table 4 shows the percentage of patients who developed grade 3 or 4 neutropenia or thrombocytopenia at any time during the therapy; these data are presented by CTX dose. Patients were included if they developed this degree of myelosuppression on any course during their therapy. Dose adjustments in subsequent courses were mandated for myelosuppression, as previously detailed. At CTX 300 mg/m² daily for 3 days, almost half of the patients developed grade 4 neutropenia on at least one course. Requirement for dose reduction on subsequent courses was dependent on the dose of CTX administered. Sixty-three percent of patients treated with CTX 500 mg/m² required dose reduction, as did 60% of patients treated initially with CTX 350 mg/m². However, when CTX was initiated at 300 mg/m², only 29% of patients required dose de-escalation.

There was a trend for increased myelosuppression in previously treated patients. Neutropenia less than 500/µL in at least one cycle was noted in 58% of previously treated patients compared with 41% of previously untreated patients (P = .13). Similarly, neutropenia less than 1,000/µL occurred in 88% of previously treated patients compared with 74% of previously untreated patients (P = .095).

Not unexpectedly for a regimen whose major side effect was myelosuppression, infections or fever of unknown origin occurred in almost half the patients. Documented sepsis or pneumonia was noted in 25% of patients at some time during the therapy. Fever of unknown origin, frequently associated with neutropenia and requiring hospitalization, was observed in another 25% of patients. Since myelosuppression and/or infection resulted in subsequent dose reductions, when infections are shown as a percentage of total courses given, they were observed in only 10% of all cycles of chemotherapy (Table 3). Significant infections were seen in only 18% of patients not refractory to fludarabine with or without alkylating agents compared with 48% in fludarabine-refractory patients (P < .001). Six atypical infections were noted, including one case of *Pneumocystis carinii* pneumonia, one cryptococcal bronchitis, one cryptococcal meningitis, one *Vibrio* sepsis, one strongyloidiasis, and one infectious episode with cytomegalovirus. Two of those patients were also receiving corticosteroids. Seven patients (5%) developed herpes zoster infections, and 10 patients (8%) had reactivation of herpes simplex. Mild eosinophilia in the peripheral blood (≥5%) was seen in 46% of patients treated with fludarabine and CTX. This phenomenon of eosinophilia in the setting of nucleoside analog therapy has been described previously. Interestingly, eosinophilia seemed to be associated with response: 90% of patients with ≥5% eosinophils responded to therapy, compared with 55% of the others.

### Remission Duration and Survival

The median time to progression in responding patients who had previously received fludarabine and alkylating agents was 20 months (Fig 1). Remissions were significantly longer for patients who had only prior alkylating agents, with a median time to progression of 33 months. The median time to progression has not been reached among previously untreated patients achieving PR or CR, with a median follow-up of 41 months (Fig 1). The median survival of previously untreated patients has not been reached (Fig 2). The estimated median survival was 38

### Table 3. Toxicities in Patients Receiving Fludarabine and Cyclophosphamide (N = 128)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>% of Patients</th>
<th>% of Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue/aches</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Fever or infections</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

### Table 4. Myelosuppression by Cyclophosphamide Dose (N = 128)

<table>
<thead>
<tr>
<th>CTX Dose (mg/m²/day × 3)</th>
<th>AGC</th>
<th>Plts</th>
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<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>500</td>
<td>88</td>
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</tr>
<tr>
<td>350</td>
<td>96</td>
<td>48</td>
</tr>
<tr>
<td>300</td>
<td>75</td>
<td>48</td>
</tr>
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Abbreviations: AGC, absolute granulocyte count; Plts, platelets.
agents, the response rates were 45% to 65%. Historical studies of fludarabine in patients previously treated with alkylating agents showed that the combination of fludarabine and CTX seems to be significantly better than those reported with single-agent fludarabine in CLL salvage. In phase II studies, the combination of fludarabine and CTX was fractionated over 3 days, rather than being given as a bolus, on the basis of in vitro data showing that repair of DNA crosslinks after exposure to 4-HC is accomplished quickly, while most crosslinks no longer detectable after 6 hours. The initial CTX dose of 500 mg/m² daily for 3 days was very myelosuppressive and was subsequently reduced to a final dose of 300 mg/m² daily for 3 days. CTX was fractionated over 3 days, rather than being given as a bolus, on the basis of in vitro data showing that repair of DNA crosslinks after exposure to 4-HC is accomplished quickly, with most crosslinks no longer detectable after 6 hours.

The results with the fludarabine and CTX combination appear to be significantly better than those reported with single-agent fludarabine in CLL salvage. In phase II studies of fludarabine in patients previously treated with alkylating agents, the response rates were 45% to 65%.

DISCUSSION

The two most important classes of agents in the treatment of B-cell CLL are nucleoside analogs and alkylating agents. Combining these two groups of agents to improve prognosis in CLL is appealing. Preclinical studies suggested that the formation of DNA crosslinks after exposure to activated CTX in vitro was prolonged with concomitant use of fludarabine, presumably because of fludarabine-induced inhibition of DNA repair enzymes. Thus, both clinical and laboratory rationales support the use of the combination of fludarabine and CTX. Because the single-agent toxicities were similar (myelosuppression, immunosuppression), we elected to use about two thirds of the single-agent dose of fludarabine in the combination (ie, 3 days of fludarabine 30 mg/m² daily). The initial CTX dose of 500 mg/m² daily for 3 days was very myelosuppressive and was subsequently reduced to a final dose of 300 mg/m² daily for 3 days. CTX was fractionated over 3 days, rather than being given as a bolus, on the basis of in vitro data showing that repair of DNA crosslinks after exposure to 4-HC is accomplished quickly, with most crosslinks no longer detectable after 6 hours.

The results with the fludarabine and CTX combination appear to be significantly better than those reported with single-agent fludarabine in CLL salvage. In phase II studies of fludarabine in patients previously treated with alkylating agents, the response rates were 45% to 65%.

Historical data from our studies among such patients indicate a 58% response rate. Since fludarabine became available in 1987, patients previously treated only with alkylating agents are now referred infrequently to our institution and constitute a minority of patients on protocol. A more commonly referred group are patients who have been previously treated with alkylating agents and fludarabine and who are often resistant to either their initial or reinduction course. Patients who have responded to alkylating agents and fludarabine and have then relapsed have approximately a 30% to 35% response rate if retreated with single-agent fludarabine (unpublished data). An even more refractory group are those who are fludarabine-resistant (either on initial or subsequent treatment). These patients have a very poor prognosis and a median survival of less than 1 year. Most combination chemotherapy regimens produce a response rate of ≈ 15% in fludarabine-refractory patients, and new therapies are urgently needed for that subset. The response rate of 38% to the combination of fludarabine and CTX is significant in fludarabine-refractory patients and supports the synergistic activity of fludarabine and CTX. Although this response rate in refractory patients is higher than any other regimen we have used previously, most of these remissions are PRs with a median time to progression of less than 1 year. Thus, most patients will progress within several months of completion of therapy. In addition, administration of the combination to refractory patients was complicated by a high incidence of myelosuppression and infections, with 48% of these patients experiencing at least one hospitalization for sepsis with or without pneumonia. New therapies for patients failing alkylating agents and fludarabine are still urgently needed.

Previously untreated patients receiving fludarabine as their initial therapy have a high response rate of 70% to 80%, and only a large trial could demonstrate an improvement in overall response rate with combination chemotherapy. 1,2 In this group of patients, the aim was to increase the CR rate, which, using the revised NCI Working Group guidelines for response, is approximately 30% in our own database. This is very similar to the 27% CR rate documented with fludarabine therapy in the large intergroup trial in which previously untreated patients were randomized to fludarabine or chlorambucil. 2 With fludarabine and CTX, the CR rate was 35% in these patients, not improved over what would have been expected with fludarabine alone. Most patients who achieved nodular PR had one or two nodules on bone marrow biopsy and seemed to have minimal disease. Interestingly, in previous single-agent fludarabine trials, patients who had nodular remissions after six cycles generally did not improve with further therapy to a true CR, which suggests that the characteristics of the cells forming these nodules may be different from other cells in
CTX; only 8% of patients achieving CR had CD5+ B cells at the time CR is documented. With fludarabine and CTX, only 8% of patients achieving CR had CD5+ B cells in the marrow, compared with 33% of previously untreated patients receiving fludarabine with or without prednisone (unpublished data). This suggests that although the CR rate was not higher with the combination, these were “better quality” CRs which may be more durable because of less residual disease detectable at the time of remission. The median time to progression in these untreated patients who received fludarabine and CTX has not been reached at a median follow-up of 41 months, compared with 30 months for untreated patients responding to single-agent fludarabine with or without prednisone (Fig 3). However, the median follow-up of surviving patients in the historical control group is 9.3 years; difference in time to progression might be minimized with longer follow-up of patients treated with fludarabine and CTX.

Although fludarabine produces little extramedullary toxicity, nausea, in particular, and vomiting were noted more frequently with the combination than with single-agent fludarabine. Similar to the experience with single-agent fludarabine therapy, the major side effects encountered with the combination were myelosuppression and infections. Twenty-five percent of patients were unable to complete the planned six courses because of cumulative myelosuppression. Infections were common, and serious infections, including bacteremia and/or pneumonia, were seen in 25% of patients, although mandated dose reductions for subsequent courses resulted in only 7% of total courses complicated by such infections. Atypical infections were rare with the combination.

Two groups have combined fludarabine with chlorambucil in a phase one trial. Weiss et al gave the combination to 15 heavily pretreated patients with CLL. The predominant toxicity was thrombocytopenia, with 73% having ≥ grade 3 toxicity. The maximum-tolerated dose was fludarabine 15 mg/m²/d for 5 days with chlorambucil 20 mg/m² on day 1. Clearly, the concomitant administration of chlorambucil necessitated dose reductions of fludarabine. Elias et al also conducted a phase I trial combining these two agents. Twenty-one pretreated patients received chlorambucil on day 1 and fludarabine on days 1 through 5 every 28 days. The maximum-tolerated dose was chlorambucil 15 mg/m² and fludarabine 20 mg/m². The dose-limiting toxicity was thrombocytopenia. The authors concluded that although remissions were observed, “it was impossible from this study to determine whether the combination was better than fludarabine alone in this heavily pretreated population” and suggested further exploration of this combination in the large randomized intergroup trial. In 1995, Rai et al published the first abstract describing this trial of fludarabine versus chlorambucil versus fludarabine and chlorambucil. In the combination arm, both drugs were given at 20 mg/m²; this arm was closed early due to a high hematologic toxicity rate. Further details of this study await final publication of the manuscript.

Recently, Flinn et al published results of the combination of fludarabine and CTX in the treatment of CLL and low-grade lymphoma. They administered CTX 600 mg/m² on day 1 with fludarabine 20 mg/m² on days 1 through 5 to 60 patients with previously untreated disease. All patients in this trial received supportive care with granulocyte colony-stimulating factor and prophylactic trimethoprim sulfamethoxazole. Seventeen patients had CLL, six (35%) with advanced stage (Rai 3-4) disease. All patients with CLL responded to treatment; the CR rate was 47% (95% confidence interval, 0.23 to 0.72). Unlike in the present trial, no episodes of nausea or vomiting were noted. This might be due to the lower dose of CTX administered or the bolus schedule used. Myelosuppression was uncommon and, similarly, serious infections were rare. In the current trial, grade 3 or 4 myelosuppression (at the 300-mg/m² dose of CTX) occurred in 70% of previously untreated patients, but growth factor support was not used. The German CLL study group used fludarabine 30 mg/m²/d and CTX 250 mg/m²/d on days 1 to 3 every 28 days for a maximum of six cycles, a regimen similar to the one described in the current study. Thirty-two patients with CLL were treated; 20 of these patients had received prior therapy. Twenty-two (88%) of 25 assessable patients responded; three CRs were noted. Grade 3 or 4 leukopenia and thrombocytopenia occurred in seven and two patients, respectively. No severe infections were described. Thus, the combination of fludarabine and alkylating agents requires reduction in fludarabine...
dose-intensity; preliminary data from trials utilizing fludara-
bine and CTX suggest that response rates are higher than
those expected with single-agent fludarabine.

In summary, the fludarabine and CTX combination pro-
duced a high response rate in patients with CLL receiving
this treatment as salvage therapy. One third of patients
refractory to single-agent fludarabine and alkylating agents
responded, although most of these remissions were partial.
The use of fludarabine and CTX did not significantly
increase the CR rate in previously untreated patients over
that documented in other studies, both from M.D. Anderson
Cancer Center and the Intergroup trial. However, minimal
residual disease, defined by CD5⁺ B cells at the time of CR,
was very low and these CRs may be more durable. The
toxicity of fludarabine 30 mg/m² with CTX 300 mg/m² was
acceptable in terms of recommending this dose for further
trials. Dose reductions were required subsequently in 29%
of patients beginning therapy at this dose level. Myelosup-
pression and infections remain the most important compli-
cations in the treatment of CLL.

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