# Long-Term Follow-up of Patients With Chronic Lymphocytic Leukemia Treated With Fludarabine as a Single Agent

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**The clinical response and survival of 113 patients with at least 3-year follow-up after treatment with fludarabine as a single agent for chronic lymphocytic leukemia has been evaluated. Seventy-eight patients were previously treated and 35 were untreated. The response to therapy and survival were strongly correlated with the degree of previous therapy, the stage of disease, and whether or not the patients were refractory to alkylating agents. Other characteristics associated with survival were the age of the patient and the serum albumin level at the start of therapy. The median time to progression of responders who had not received prior therapy was 33 months and was 21 months for previously treated patients. Survival after progression of disease was also strongly correlated with the degree of prior therapy. No successful salvage regimen after initial fludarabine therapy was shown for patients refractory to alkylating agents, although fludarabine achieved further remissions in patients who had received fludarabine as their initial treatment or were not refractory to alkylating agents. The morbidity of patients in unmaintained remission on discontinuation of fludarabine was low, with less than one episode of infection per patient-year at risk. The morbidity during this time was correlated with clinical response and whether the patients had received prior therapy. Although fludarabine is a very effective cytoreductive regimen, most patients, including those who achieved true complete remissions, will have recurrent disease. Longer follow-up and comparative trials are required before the effect of fludarabine on survival is shown.**


THE TRADITIONAL approach to the management of chronic lymphocytic leukemia (CLL) is based on the activity of alkylating agents and corticosteroids against the disease. Chlorambucil alone or in combination with corticosteroids has become standard initial therapy and is associated with a complete and partial response rate of 40% to 77% in previously untreated (UNT) patients.[1-3] No effective therapy 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 and 2-chlorodeoxyadenosine, and the adenosine deaminase inhibitor 2-deoxycoformycin.[4-6] Fludarabine (9-$\beta$-D-arabinofuranosyl-2-fluro-adenine monophosphate) is a fluorinated analog of ara-adenine that is relatively resistant to deamination by adenosine deaminase.[7] Based on the ability of fludarabine to cause lymphopenia, the drug was used in phase I to II studies and Grever et al[8] and Leiby et al[9] reported activity in lymphoma and CLL. Subsequently, a variety of schedules have been used in the management of CLL.

We have reported activity of fludarabine in both previously treated patients and previously UNT patients.[10,11] Fludarabine appears to be the most active single agent to have been evaluated in CLL. This publication reviews the overall response rate, survival, time-to-progression (TTP), long-term morbidity, and outcome of salvage therapy in previously UNT and previously treated patients who received fludarabine as a single agent.

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## PATIENTS AND METHODS

One hundred thirteen patients with CLL were entered on the study of fludarabine as a single agent between March 1985 and June 1989 (minimum 3-year follow-up). The median age was 62 years, with a range from 32 to 84 years. Seventy-six patients were men. The median white blood cell (WBC) count was 70,600/$\mu$L with a range of 4,500 to 594,000/$\mu$L, median marrow cellularity was 85%, and median percentage of lymphocytes in the marrow was 87%. The median time from initial diagnosis to treatment was 47 months with a range of 1 to 346 months. While initial studies were conducted on patients who were refractory to conventional therapy, subsequently all previously treated patients were entered on study regardless of refractory status.[10] (Refractory disease was defined as failure to obtain a complete or partial response after therapy with an alkylating agent regimen or development of progressive disease while patients were still receiving alkylating agents.) Thereafter, previously UNT patients received therapy with fludarabine as a single agent.[11] Initially UNT patients who had Rai stage III and IV disease were entered and subsequently patients with progressive Rai stage 0 to II disease. The preliminary results of the first 68 previously treated patients and the first 33 previously UNT patients have been published.[10,11] The median number of courses was six with a range of 2 to 15.

*Diagnostic criteria.* All patients had documentation of lymphocytosis with an absolute lymphocyte count greater than 10,000/$\mu$L on at least two previous occasions 1 month apart and had more than 30% lymphocytes in the bone marrow (BM). The diagnosis on all patients and the percentage of lymphocytes was confirmed by two pathologists. The disease in each patient was assigned a Rai and Binet stage at the time of initiation of fludarabine treatment. Pretreatment evaluation included a medical history and physical examination to document tumor measurements of liver, spleen, and lymph nodes, complete blood cell (CBC), differential, WBC, and platelet counts and a chemical survey. The BM aspiration and biopsy were performed within 1 month preceding the onset of fludarabine treatment. Most patients had surface-marker analysis providing evidence of a monoclonal B-cell proliferation.[10,11]

Guidelines for response were developed by the National Cancer Institute (NCI Working Group) for CLL.[12] Table 1 lists the NCI criteria of response. Although this classification allows for residual lymphoid nodules or infiltrates on BM biopsy to be classified as complete remission (CR), we have decided to subclassify the complete responders as to whether residual nodules and/or interstitial infiltrates persisted in the BM (CR-Nod) or whether a normal BM biopsy pattern

**Table 1. Definition of Clinical Response for Patients With B-CLL**

| | CR* | PR† | PD |
|---|---|---|---|
| Physical exam | | | |
| Nodes | None | ≥50% decrease | ≥50% increase, new nodes |
| Liver/spleen | Not palpable | ≥50% decrease | ≥50% increase, newly palpable |
| Symptoms | None | N/A | N/A |
| Peripheral blood | | | |
| Neutrophils | ≥1,500/μL | ≥1,500/μL or >50% improvement from baseline | —‡ |
| Platelets | >100,000 μL | >100,000 μL or >50% improvement from baseline | —‡ |
| Hemoglobulin (untransfused) | >11.0 g/dL | >11.0 g/dL or >50% improvement from baseline | —‡ |
| Lymphocytes | ≤4,000/μL | ≥50% decrease | ≥50% increase |
| BM | <30% lymphocytes | N/A | N/A |

Abbreviation: N/A, not applicable.

* Complete remission (CR) requires fulfillment of all criteria for a duration of >2 months, at which time a BM aspirate and biopsy are required to document response as complete.

† Partial remission (PR) requires fulfillment of the above-noted decrease in circulating lymphocytes, regression in either adenopathy and/or hepatosplenomegaly, and one other parameter listed above for a duration of >2 months.

‡ In the absence of other indices of clinical progression, the presence of a ≥2 g/dL decrease in hemoglobin, or ≥50% decrease in platelet count and/or absolute granulocyte count, will not exclude a patient from continuing the study.

was found (CR-Bx). Patients were considered to have resistant disease if they had achieved less than a partial remission (PR) after at least three courses or had progressive disease at any stage of treatment (more than 25% increase in nodes, liver, spleen, or WBC count). Treatment was administered in blocks of three courses after which patients were reevaluated. As this was a phase I to II study, treatment was discontinued after varying numbers of courses after patients achieved a CR-Bx or CR-Nod. In patients who achieved a complete response or partial response, progressive disease was considered to have occurred when the absolute lymphocyte count had increased to more than 10,000/μL on two occasions 1 month apart, or the percentage of BM lymphocytes increased above 50%. TTP was measured from the initiation of fludarabine therapy. Reenlargement of nodes, liver, or spleen was considered evidence of progressive disease. Patients who achieved only a partial response had to have a 50% increase in amount of any residual disease or appearance of new sites of disease.

*Salvage therapy.* All patients who had been previously UNT and responded to fludarabine were retreated with fludarabine when progressive disease requiring therapy was noted. Patients who had had prior therapy (prior Rx) before fludarabine and had responded, were subsequently retreated with fludarabine in some cases or a variety of other regimens in other cases.

## RESULTS

The response rate to fludarabine varied according to whether or not the patients had been treated previously (78 patients) and whether or not they were considered to be refractory to alkylating agents (Table 2). The response rate was also related to the extent of prior treatment being lower in more extensively treated patients. Advanced Rai stage and age greater than 70 years were also adverse prognostic factors for response in each group and the Binet stage for the combined group of 113 patients. Nineteen (63%) of the 30 CR patients in the prior treated group and 13 (50%) of the 26 CRs in the untreated groups had residual lymphoid infiltrates.

Survival was also dependent on whether or not the patients had been treated previously and were or were not refractory to alkylating agents (Fig 1). The median survival of previously UNT patients has not been reached, and for the previously treated (not refractory) patients median survival was 29 months and for the previously treated (refractory) patients, 9 months. Nine patients in the untreated group have died, 5 nonresponders (infection, 3; hemorrhage, 1; and lung cancer, 1) and 4 responders. Two of the responders died of large cell lymphoma that was their initial relapse of CLL, and 2 died after relapse, 1 of lung cancer and 1 of infection with refractory CLL. Survival correlated with response to therapy (Fig 2), but was only slightly greater for the CR-Bx patients (median 46+ months) than CR-Nod (median 41 months) ($P$ = .03) (Table 3). Survival of CR-Bx and CR-Nod patients were both superior to the survival of PR patients (median 34 months) (CR *v* PR, $P < .05$; CR-Nod *v* PR, $P = .10$). No difference in survival was noted between the CR-Bx and CR-Nod patients overall ($P = .29$) or in the UNT or treated groups separately. No difference was noted for the survival of the PR patients compared with the CR-Bx or CR-Nod patients in the previously treated groups. The two PR patients in the UNT group had shorter survival times (35, 37 months) than the CR-Bx or CR-Nod patients. More patients with PRs had been previously treated. Thus, the favorable impact of CR on response appears to be caused by the asymmetric distribution of complete and partial responses in the prior treated and UNT groups. Survival was also associated with the Rai (Fig 3) and Binet stages documented before fludarabine.

Seventeen of the 30 failing patients (10 early deaths excluded) went on to receive alternate therapy, 4 with VAD (vincristine, doxorubicin, and dexamethasone), 3 with ara-C and cisplatinum combinations, 2 with chlorambucil and prednisone, 1 with pentostatin, 1 with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 1 with 2-chloro-deoxyadenosine, and 6 with miscellaneous other regimens. The patient treated with CHOP was the only patient who obtained a response (PR). This patient was initially re-

**Table 2. Response to Fludarabine by Patients by Pretreatment Characteristics and Prior Treatment Status**

| | | No Prior Rx | | | Prior Rx | | |
|---|---|---|---|---|---|---|---|
| Characteristic | Value | No. Patients | CR% | CR + PR% | No. Patients | CR% | CR + PR% |
| Prior Rx | Untreated | 35 | 74 | 80 | — | — | — |
| | Yes (refract) | — | — | — | 50 | 28 | 38 |
| | Yes (non-ref) | — | — | — | 28 | 57 | 93 |
| No. prior regimens | 1 | — | — | — | 22 | 55 | 82 |
| | 2-3 | — | — | — | 40 | 38 | 51 |
| | >3 | — | — | — | 16 | 19 | 44 |
| Rai stage | 0 | 2 | 100 | 100 | 1 | 100 | 100 |
| | I-II | 18 | 78 | 84 | 30 | 43 | 76 |
| | III-IV | 15 | 67 | 74 | 47 | 34 | 51 |
| Binet stage | A | 17 | 88 | 94 | 22 | 46 | 64 |
| | B | 11 | 54 | 54 | 22 | 41 | 77 |
| | C | 7 | 72 | 86 | 34 | 32 | 41 |
| Age—yrs | <60 | 10 | 70 | 70 | 38 | 42 | 61 |
| | 60-69 | 19 | 63 | 74 | 34 | 38 | 62 |
| | ≥70 | 6 | 50 | 50 | 6 | 17 | 17 |
| Albumin (G%) | ≤3.5 | 1 | 100 | — | 9 | 11 | 11 |
| | 3.6-4.0 | 11 | 82 | 91 | 19 | 37 | 54 |
| | ≥4.1 | 23 | 70 | 74 | 50 | 44 | 64 |

Abbreviation: Rx, treatment.

fractory to therapy with fludarabine. All except 1 of these patients were Rai stage III or IV when administered salvage therapy. Survival after failing initial treatment with fludarabine was poor (median 9 weeks) with only five patients surviving 1 year (three previously UNT).

Ten responders in the untreated group remain in continued complete remission, and two have progressed and have not been retreated. Two patients have developed a large cell lymphoma, and one patient Hodgkin's disease (now in CR of both diseases). Fifteen of the 28 responders in the UNT group have developed progressive disease and 13 have been retreated with fludarabine (Table 4). Eight (61%) have obtained a CR, and 3 (23%) a PR. The two nonresponding patients were treated with intermittent fludarabine (one 5-day course each 2 to 4 months) in a palliative mode and neither patient responded. The response rate according to the Rai stage at the start of salvage therapy was stage 0 (5/5), stage I (3/4), stage II (1/1), stage III (1/1), and stage IV (1/2) patients.

The salvage treatment for the prior treated group was more diverse and the results less satisfactory. Six of the 45 previously treated responders remain in remission (CR-Bx, 2; CR-Nod, 3; PR, 1) and 32 developed progressive disease of whom 27 have received salvage therapy (Table 4). The other five patients, one of whom is alive, did not receive any further treatment. Four patients have died without developing progressive disease: suicide, cirrhosis, cytomegalovirus (CMV) pneumonia, and pneumonia of unknown pathogen being the cause in one patient each. One patient developed acute myelogenous leukemia (AML) and two patients large cell lymphoma. Four (27%) of 15 patients retreated with fludarabine have responded (3 CRs and 1 PR). All four responders were in the nonrefractory subcategory before their initial fludarabine and were Rai stage 0 to II at the time of salvage therapy. No other

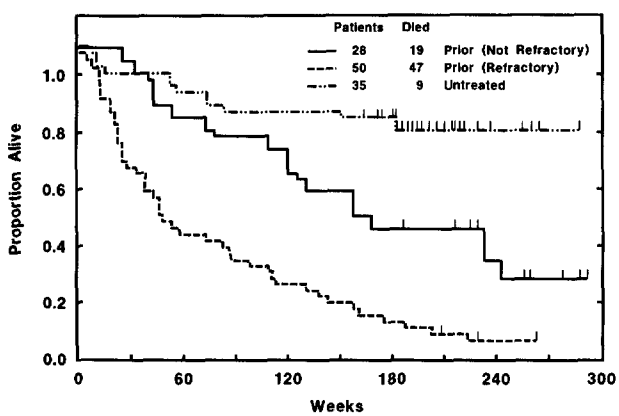


Fig 1. Fludarabine in CLL: survival by prior treatment and refractory status.

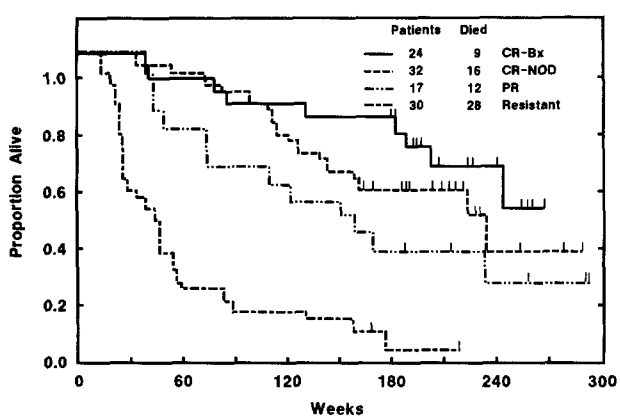


Fig 2. Fludarabine in CLL: survival by response.

**Table 3. Characteristics Associated With Survival According to Prior Treatment Status**

| Characteristic | Value | Median Survival (mos) Untreated | Treated | Total |
|---|---|---|---|---|
| Prior Rx | No | 66+ | | — |
| | Yes (refract) | | 9 | — |
| | Yes (non-ref) | | 29* | — |
| No. prior regimens | 0 | 66+ | — | 66+ |
| | 1 | — | 46 | 46 |
| | 2-3 | — | 9* | 9* |
| | >3 | — | 12 | 12 |
| Rai stage | 0-II | 59+† | 19 | 46* |
| | III-IV | 66+ | 10 | 18 |
| Binet stage | A | 66+ | 27 | 54 |
| | B | 61+ | 17† | 19* |
| | C | 50+ | 9 | 11 |
| Response | CR-Bx | 61+ | 29 | 56+ |
| | CR-Nod | 66+ | 31 | 36 |
| | PR | 34 | 24 | 27 |
| Age—yrs | <60 | 66+ | 24 | 29 |
| | 60-69 | 61+* | 11 | 28† |
| | ≥70 | 2 | 4 | 4 |
| Albumin (G%) | ≤3.5 | 16 | 2 | 5 |
| | 3.6-4.0 | 66+ | 10* | 19* |
| | ≥4.1 | 60+ | 27 | 34 |

Abbreviation: Rx, treatment.
* $P < .01$ log rank.
† $P < .05$ log rank.

**Table 4. Response (CR + PR) to Salvage Therapy of Patients Who Initially Responded to Fludarabine**

| Salvage Regimen | Initial Response to Fludarabine CR-Bx | CR-Nod | PR | Total |
|---|---|---|---|---|
| Untreated group | | | | |
| Fludarabine | 4/4 (100%) | 6/8 (75%) | 1/1 (100%) | 11/13 (85%) |
| Prior Rx group | | | | |
| Fludarabine | 2/3 (67%) | 0/7 (—) | 2/5 (40%) | 4/15 (27%) |
| Ara-C + cisplatin | 0/3 (—) | 0/1 (—) | 0/1 (—) | 0/5 (—) |
| Other | 0/1 (—) | 0/2 (—) | 0/4 (—) | 0/7 (—) |

regimen has obtained a response. The TTP after salvage therapy in the four responders was substantial, being 6, 22, 24, and 31 months. Patients with a longer TTP had a higher response rate than those with a shorter TTP but, as this was highly correlated with extent of prior history, no final conclusion regarding the prognostic relevance of the measurement could be drawn. The response rate for patients with a TTP of less than 12 months was 1/9 (0/7 prior Rx, 1/2 UNT), with a TTP of 12 to 23 months was 6/18 (4/16 prior Rx, 2/2 UNT), and with a TTP greater than 24 months was 8/13 (0/4 prior Rx, 8/9 UNT).

*TTP.* The median time to development of progressive disease (TTP) of the responders (CR-Bx, CR-Nod, and PR) was 26 months. Several characteristics were associated with a short TTP. The responders were more likely to develop progressive disease according to their prior treatment status (Fig 4), the amount of prior treatment, and if they had achieved only a PR or CR-Nod compared with those with a CR-Bx ($P < .01$) (Table 5). The stage before the initiation of fludarabine therapy, age, and serum albumin level were not associated with TTP. Survival of responders after developing progressive disease was strongly associated with prior treatment and the refractory status (Fig 5).

The 73 responders enjoyed good health after discontinuation of fludarabine until progression of their disease occurred. Thirty-nine episodes of infection were observed during that time: pneumonia (7), urinary tract infection (8), soft tissue infections (8), bronchitis/sinusitis (5), dermatomal herpes zoster (5), fever of unknown origin (3), and tuberculosis, hepatitis, and influenza in 1 each. The incidence of febrile episodes for the 73 patients (calculated as the number of episodes divided by the sum of the times from discontinuation of fludarabine to the onset of progressive disease) was 0.34 episodes per year at risk (Table 6). The incidence was lower for the CR-Bx patients (0.22) than those with CR-Nod (0.40) or a PR (0.59) and for previously UNT patients (0.23) than for previously treated patients (0.48). The risk of infectious episodes was increased during the time from documen-

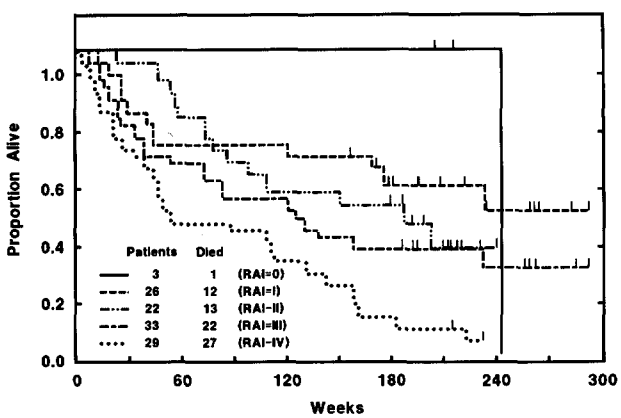


Fig 3. Fludarabine in CLL: survival by Rai stage prior to fludarabine.

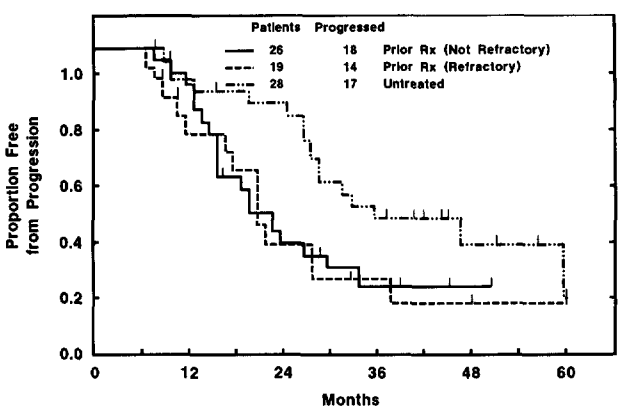


Fig 4. Fludarabine in CLL: TTP by prior treatment and refractory status.

**Table 5. Characteristics Associated With Time to Progression of Responders**

| Characteristic | Values | Median TTP (mos) Untreated | Treated | Total |
|---|---|---|---|---|
| Prior Rx | No | 32 | | — |
| | Yes (refract) | | 18 | — |
| | Yes (non-ref) | | 17 | — |
| No. prior regimens | 0 | 32 | — | 32 |
| | 1 | — | 22* | 22† |
| | 2-3 | — | 19 | 19 |
| | >3 | — | 15 | 15 |
| Rai stage | 0-II | 31 | 15 | 27 |
| | III-IV | 28 | 18 | 24 |
| Binet stage | A | 31 | 21 | 27 |
| | B | 19 | 14 | 15 |
| | C | 26 | 19 | 24 |
| Response | CR-Bx | 46* | 20 | 35† |
| | CR-Nod | 27 | 20 | 22 |
| | PR | 24 | 12 | 13 |
| Age—yrs | <60 | 28 | 19 | 20 |
| | 60-69 | 31 | 18 | 26 |
| | ≥70 | 28 | 32 | 28 |
| Albumin | ≤3.5 | 16 | 7 | 7 |
| | 3.6-4.0 | 28 | 11 | 24 |
| | ≥4.1 | 35 | 19 | 23 |

Abbreviation: Rx, treatment.
* $P < .05$ log rank.
† $P < .01$ log rank.

tation of progressive disease until the reinitiation of more treatment (1.06). Infections during this time were noted only in the previously treated patients: pneumonia (2), sinusitis (4), fever of unknown origin (3), herpes zoster (3), and tuberculosis, influenza, and skin infection (one each).

## DISCUSSION

Earlier studies have shown the clinical efficacy of fludarabine as a single agent in the management of previously UNT and previously treated patients with CLL.[4,8,10,11,13] However, in a disease such as CLL with an indolent natural history, the outcome of treated patients over a long-term follow-up period is essential before conclusions can be drawn as to efficacy.

This report summarizes our experience with fludarabine as a single agent in previously UNT and treated patients with CLL with a minimum of 3-year follow-up. While response to patients who have been previously treated was high for fludarabine, a striking impact of the patient's preceding treatment history is obvious. The UNT patients had a substantially higher CR + PR percentage with the majority of patients achieving a CR using the rigorous NCI criteria. In addition, there was a significant impact of the patients' previously documented responsiveness to alkylating agents. As in lymphomas, our patients with CLL who were refractory had a significantly lower response rate than patients who were potentially still sensitive to alkylating agents. This is borne out by the impact of the number of prior treatment regimens on response where there is a linear trend for lower response to patients who have had more prior treatment regimens.

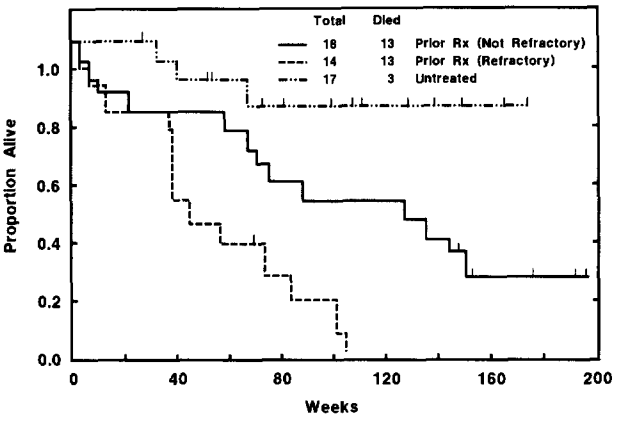


**Fig 5. Fludarabine in CLL: survival after progression.**

This association of response with prior treatment is in addition to the impact of the Rai and Binet stages. Age did not have a significant impact on response apart from a lower response rate being noted in the small number of patients over 70 years of age who were entered on the studies. In addition, serum albumin was associated with response rate. Too few patients were entered on the study to undertake a meaningful multivariate analysis that will be applied to a larger patient population that have now been treated with a variety of fludarabine regimens.

The characteristics that were associated with response were also associated with survival. Survival in the previously treated group of patients was strongly associated with their refractory status and the number of prior treatment regimens that the patients received. There was a significant association of Binet stage with survival in the previously treated patients and an association of serum albumin level with survival. The good overall survival of the previously UNT population with a projected 75% 5-year survival rate prevents any meaningful association between survival and other characteristics. The early death rate in elderly patients and early death rate in Rai stage III and IV patients was associated with a significant survival disadvantage of those patients. As opposed to a

**Table 6. Episodes of Infection in Responding Patients After Discontinuation of Therapy Until Progressive Disease According to Response and Prior Treatment Status**

| Response | Prior Rx | No. Patients | Episodes | Months at Risk* | Episodes/ Year at Risk |
|---|---|---|---|---|---|
| CR-Bx | No | 13 | 6 | 445 | 0.16 |
| | Yes | 11 | 6 | 191 | 0.38 |
| | Total | 24 | 12 | 636 | 0.23 |
| CR-Nod | No | 13 | 7 | 258 | 0.32 |
| | Yes | 19 | 11 | 282 | 0.47 |
| | Total | 32 | 18 | 540 | 0.40 |
| PR | No | 2 | 1 | 31 | 0.39 |
| | Yes | 15 | 8 | 151 | 0.64 |
| | Total | 17 | 9 | 182 | 0.59 |

Abbreviation: Rx, treatment.
* Discontinuation of Rx until progressive disease noted.

number of other studies, there was no strong association with survival according to whether the patients had a CR-Bx, CR-Nod, or PR in either of the previously UNT or previously treated patient populations. Thus, the impact of response on survival is still arguable. There was a trend for a better survival according to response within the total group of 113 patients ($P = .09$).

A significant difference in TTP was found for the UNT patients versus the previously treated patients and for patients who had had a CR-Bx who had a significantly longer TTP than CR-Nod and PR patients. Surprisingly, the Rai and Binet stages had no significant impact on TTP once the patients had achieved a CR or PR. A significant impact on survival of the previously treated patients was the lack of response to salvage therapy in the refractory group and a significantly shorter survival after progression for the refractory group than for the prior treated nonrefractory group. Patients with previously UNT disease who received fludarabine had an excellent response to salvage therapy and are projected to have a long survival after progression.

The lack of response to salvage therapy in the previously treated patients suggests that there is no effective regimen that can be applied after fludarabine at this time. 2-Chlorodeoxyadenosine (2CDA) has not been systematically studied in this group of patients.[5,14] The short survival after progression shows an urgent need for new, effective agents in refractory CLL. The short survival after progression suggests that patients should be continued on fludarabine or have some alternate postremission therapy to try to prolong survival after they obtain a remission as response to treatment after relapse and survival after relapse is so short. A recent report of a very high rate of cytoreduction after 2CDA therapy in CLL patients reportedly refractory to fludarabine awaits confirmation.[15]

One of the questions in the previously treated patients is whether the high response rate to fludarabine has translated into a survival advantage. Comparable patient populations are scarce in the literature.[16-18] Our previous experience with the POACH (prednisone, vincristine, ara-C, cyclophosphamide, and daunorubicin) regimen in a somewhat comparable patient population suggests that the early survival is somewhat better for the fludarabine-treated patients but the long-term survival is similar.[19]

Additional studies need to be conducted in previously UNT patients receiving fludarabine as a single agent. There is obviously a high complete remission rate. The TTP is somewhat longer than for the previously treated patient populations and there is a high salvage rate on reinduction therapy, raising questions as to the duration of treatment in these patients and whether postremission therapy should be undertaken. We have shown with fludarabine + prednisone regimens that the time to progression is superior for patients who achieve a CR-Bx than those with a CR-Nod.[20] Whether this is related to a different natural history of the patients who tend to have residual nodules or the fact that CR-Bx is a "more complete" remission requires further follow-up.

Reports of the low CD4 numbers after treatment with the nucleoside analogues, fludarabine, 2-CDA, and pentostatin[21-23] raise concern regarding the probability of developing opportunistic infections while on treatment or after discontinuing therapy. CD4/CD8 data were not systematically collected in this study as it was a phase I to II study. However, it is obvious that the responders have a low overall likelihood of developing infections of any sort while they are in remission. The number of episodes per year at risk varies from 0.23 in the CR-Bx patients to 0.59 per year at risk for the PR patients. The likelihood of developing infections is lower in previously treated patients, and those with more complete remissions. The likelihood of developing infections increases after recurrence of the disease. Thus, the propensity of patients with CLL to develop infections is associated with multiple characteristics. The impact of Ig levels, primary and secondary responses to antigenic stimuli, as well as T-cell number and function requires systematic investigation.

Of the 113 patients, 4 have developed a large cell lymphoma and 1 Hodgkin's disease, the latter being a rarely reported association. The incidence of large cell lymphoma is presumably part of the natural history of CLL being reported by Han et al[24] and Harousseau.[25] We were unable to demonstrate a higher incidence in patients treated with fludarabine compared with our historical experience.[26] The patient with AML had a myelodysplastic syndrome before the diagnosis of CLL.

Long-term follow-up of patients treated with fludarabine illustrates that the response rate, survival, and TTP are associated with the degree of previous therapy. The best responses occur in patients who have been previously UNT. Relatively few patients with prior therapy who receive fludarabine are likely to remain disease free for long periods of time so that postremission therapy, whether continued chemotherapy, biologic therapy, or transplantation, is indicated. The optimal duration of fludarabine and the best strategy for postremission therapy are not known and must be established in carefully designed clinical trials. The impact on survival of fludarabine in previously treated patients and previously UNT patients is uncertain at this time but will be addressed in subsequent comparative trials by national groups. Patients who do achieve a response are able to discontinue therapy and have an excellent quality of life with a low risk of developing infections or complications of their disease during the period of remission. There is an urgent need to develop new, effective regimens for management of CLL after resistance to fludarabine has occurred.

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