EXHIBIT 2004

Long-Term Follow-Up of Patients With Chronic Lymphocytic Leukemia (CLL) Receiving Fludarabine Regimens as Initial Therapy

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One hundred seventy-four patients with progressive or advanced chronic lymphocytic leukemia (CLL) have received initial therapy with fludarabine as a single agent or fludarabine combined with prednisone. The overall response rate was 78% and the median survival was 63 months. No difference in response rate or survival was noted in the 71 patients receiving fludarabine as a single agent compared with the 103 patients who received prednisone in addition. The median time to progression of responders was 31 months and the overall median survival was 74 months. Patients over the age of 70 years had shorter survivals. Patients with advanced stage disease (Rai III and IV) had a somewhat shorter survival than earlier stage patients. More than half the patients who relapsed after fludarabine therapy responded to salvage treatment, usually with fludarabine-based regimens. Second remissions were more common in patients who had achieved a complete remission on their initial treatment. The CD4 and CD8 T-lymphocyte subpopulations decreased to levels in the range of 150 to 200/ μL after the first 3 courses of treatment. Although recovery towards normal levels was slow, the incidence of infections was low in patients in remission (1 episode of infection for every 3.33 patient years at risk) and decreased with time off treatment. There was no association of infections or febrile episodes with the use of corticosteroids or the CD4 count at the end of treatment and a poor correlation with the increase in CD4 counts during remission. Infectious episodes were less common in patients who had a complete response compared with partial responders. Richter's transformation occurred in 9 patients and Hodgkin's disease occurred in 4 patients. Five other patients died from other second malignancies. Fludarabine appears to be an effective initial induction therapy with a reasonable safety profile for patients with CLL.

THE TRADITIONAL MANAGEMENT of patients with chronic lymphocytic leukemia (CLL) needing therapy is the use of chlorambucil with or without corticosteroids.[1-4] Other alkylating agent-based regimens that have been used are cyclophosphamide, vincristine, and prednisone (CVP)[5]; cyclophosphamide, vincristine, prednisone, and adriamycin with or without ara-C (CHOP, POACH)[6,7]; cyclophosphamide, adriamycin, and prednisone (CAP)[8]; or multiple alkylating agent regimens such as the M2 regimen.[9] Comparative studies have been performed that have not demonstrated superiority of any one regimen in previously untreated patients. The response rates to therapy have varied from 50% to 80%, with the majority of the responses being partial remissions.[1-9]

More recently, the purine analogs, ¯udarabine,[10-16] 2-chlorodeoxyadenosine,[17] and pentostatin,[18] have been explored in previously treated patients with CLL. Fludarabine, in particular, had a very high response rate, with a substantial number of complete remissions in previously treated patients with CLL.[10-16] Increasingly purine analogs are being used as initial therapy for patients with CLL.[11,18,19] Two reports from the M.D. Anderson Cancer Center (MDACC; Houston, TX) using ¯udarabine with or without prednisone have already been published, but long-term follow-up data of these studies are not available.[11,20] In particular, little information has been provided regarding time to progression in responding patients and the results of re-treatment with ¯udarabine or other regimens. Randomized comparisons between ¯udarabine and chlorambucil or between ¯udarabine, CAP, and CHOP regimens[21-23] have recently been conducted in the United States and Europe.

The purpose of this report is to present an overall evaluation of the response to ¯udarabine regimens as initial therapy of patients with CLL, the response rate, toxicity, time to progression, results of re-treatment, and long-term survival.

PATIENTS AND METHODS

Three different ¯udarabine studies form the basis of this report. The ®rst used ¯udarabine at 25 to 30 mg/m^2 daily for 5 days every 4 weeks administered as part of a phase I/II clinical trial (FLU-PhI-II).[10] The next regimen was the combination of ¯udarabine at 30 mg/m^2/d for 5 days combined with prednisone at 30 mg/m^2/d for 5 days every 4 weeks (FLU+Pred).[11] After completion of the ¯udarabine + prednisone protocol, subsequent patients were treated with ¯udarabine at 30 mg/m^2/d for 5 days every 4 weeks on a current practice research protocol (FLU-CP) and are classi®ed as FLU together with the phase I-II protocol patients. In the phase I-II protocol, the number of courses was not speci®ed. In the latter 2 protocols, all patients were projected to receive 6 cycles of therapy and continue therapy until complete response or treatment failure. However, some patients discontinued treatment after achieving complete remission in less than 6 courses. Some patients who had not achieved a complete remission after 6 courses but were continuing to improve their clinical status had additional therapy. The median number of courses was 6 (range, 2 to 11). Patients were eligible for treatment if they ful®lled the National Cancer Institute (NCI) recommendations for therapy, having advanced stage disease (Rai III and IV) or progressive stage I and II disease.[24]

One hundred seventy-four patients ful®lled the criteria for treatment with Rai stage I-IV disease. The median age of the 174 Rai III-IV patients was 61 years (Table 1). Two-thirds of the patients were male and 38% had Rai stage III and IV disease. The range of times from diagnosis to treatment was wide, but the median time was 9 months. Few patients had B symptoms, and the majority of patients had performance status 0 to 1 using the Zubrod performance scale. Less than 10% of patients had a history of prior infection (Table 1).

Patients were started on treatment between 1986 and 1993. Informed

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Submitted April 30, 1997; accepted April 9, 1998.

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0006-4971/98/9204-0003$3.00/0

Table 1. Characteristics of 174 Fludarabine-Treated CLL Patients

Median age (yr) (range)	61 (25-84)
Male/female	110/64
Rai	
I/II	59/49 (108)
III/IV	38/28 (66)
Time from diagnosis to Rx	9 mo (0-346)
B symptoms	16 (9%)
Performance status (0, 1, 2)	(93, 75, 6)
WBC $\times 10^3$/mL (range)	61.7 (5.1-430.0)
Prior infection	12 (7%)

consent was obtained according to institutional guidelines. All patients had a workup including history and physical examination; complete blood counts; differential and platelet counts; sequential multiple analysis-12 (SMA-12), including liver and renal function studies; bone marrow aspiration and biopsy; and blood and marrow samples for immunophenotyping and molecular studies. The criteria required for a con®rmation of the diagnosis were a monotypic expansion of lymphoid cells $\geq 5 \times 10^3/\mu L$ morphologically consistent with CLL (small lymphocytes) in the blood for 2 months before treatment and greater than 30% lymphocytes in the bone marrow. One hundred ®fty patients were proven to be $CD5^+$, 18 were $CD5^-$ (<20%), and 6 had no immunophenotyping studies performed. Normal renal and hepatic functions (creatine <2 mg% and bilirubin <2 mg%) were required. Patients were evaluated for marrow response after each 3 courses. NCI Working Group criteria for response were used.[24] Complete remission (CR) required disappearance of all palpable disease, a neutrophil count greater than 1,500/μL, a platelet count greater than 100,000/μL, a hemoglobin level greater than 11 g/dL, and a bone marrow aspirate lymphocyte percentage of less than 30%. Patients ful®lling the criteria noted above but with persistent lymphoid aggregates or nodules in the bone marrow biopsy were classi®ed within the partial remission (PR) group as PR-Nod. Other PRs required ≥50% decrease in palpable disease as well as ≥50% improvement of all abnormal blood parameters. No bone marrow evaluation was required for determination of PR. Computerized tomography scans were not required to stage patients or evaluate response.

STATISTICAL CONSIDERATIONS

Associations between patient characteristics and response to outcome were evaluated using the χ^2 test. Cut-points for quantitative variables were those de®ning abnormal levels or other cut-points in common use. Distributions of survival and time to progression were estimated by the method of Kaplan-Meier. Survival intervals were measured from the ®rst day of chemotherapy to death from any cause. Time to progression was measured from the ®rst day of chemotherapy to the ®rst detection of relapse from CR (de®ned as>10,000 lymphocytes/μL in the peripheral blood, development of anemia or thrombocytopenia, or more than 50% lymphocytes in the bone marrow aspirate), reappearance of lymphadenopathy, hepatomegaly, splenomegaly, or extramedullary disease. Development of Richter's transformation was considered to be a relapse. Time to progression in PR patients was de®ned as ≥50% increase in size of residual abnormalities in liver, spleen, or lymph nodes, a consistently increasing lymphocyte count to a level of at least greater than 10,000/μL, or development of anemia or thrombocytopenia.

RESULTS

Response to induction regimen. The overall response rate for 174 patients treated with ¯udarabine regimens was 78%

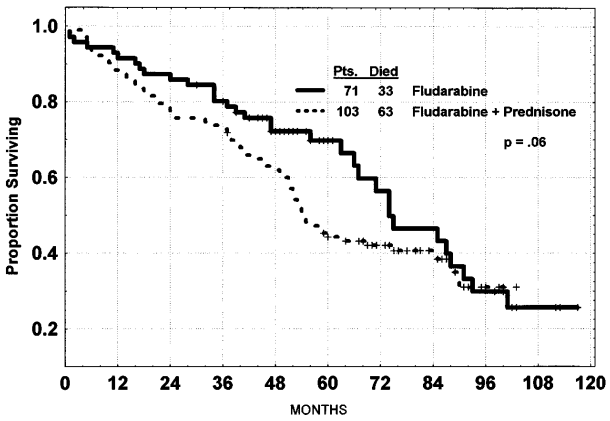


Fig 1. Survival of CLL patients treated with fludarabine alone or with prednisone. *P* value, log rank; NB median survival, 63 months.

early deaths, having died without time to recover from at least 3 courses of chemotherapy. There was no signi®cant difference in the overall response rate for the regimens, FLU (57/71 [80%]) compared with the FLU+Pred group (79/103 [77%]). However, the CR rate for FLU+Pred (24/103 [23%]) was signi®cantly less than for FLU (27/71 [38%]; $P = .04$). The vast majority of the 38 patients classi®ed as nonresponders had a signi®cant response in the peripheral blood lymphocytes (69%), nodes (57%), spleen (67%), liver (60%), and bone marrow (36%). Two of 8 patients who had a tumor CR or PR but failed to respond to treatment because of persistent cytopenia are still alive at 48 and 68 months. The survival curves show no signi®cant difference in survival for the 3 regimens, with the median values being 74, 55, and 47+ months. All patients receiving FLU-PhI-II have completed 98 months of follow-up; the median follow-up of the FLU+Pred group is 62 months and that of the FLU-CP protocol is 39 months. The curve for FLU+Pred versus the other 2 protocols combined is shown in Fig 1.

Time to progression. The median time to progression for CR, PR-Nod, and PR patients was 31 months, being signi®cantly longer for the true CR patients (37 months) compared with PR-Nod (30 months; Fig 2). No other pretreatment

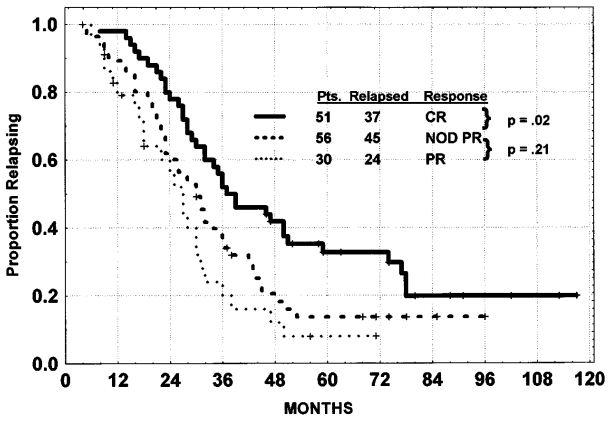


Table 2. Response to Fludarabine Regimens and Survival in Previously Untreated CLL by Pretreatment Characteristics

Characteristics	Value	No. of Patients	Median Survival (mo)	*P* Value Log Rank
Total	Ð	174	67	
Regimen	No Pred	71	74	NS
	With Pred	103	54	
Age (yr)	<60	84	75	
	60-69	64	67	<.001
	≥70	26	32	
Rai stage	I-II	108	74	.02
	III-IV	66	51	
Binet stage	A	53	74	
	B	75	66	NS
	C	46	52	
Platelets (×10³/μL)	<100,000	28	71	NS
	≥100,000	146	63	
Hemoglobin (G%)	<11	54	47	<.001
	≥11	120	74	
White blood cell count (×10³/μL)	<100,000	122	69	.10
	≥100,000	52	54	
Hepatomegaly	Yes	24	47	NS
	No	150	66	
Splenomegaly	Yes	94	56	NS
	No	80	67	
Node sites	0	23	49	
	1-2	69	67	NS
	3	81	58	
Blood urea nitrogen (mg%)	<23	145	71	
	≥23	27	33	<.001
LDH	Normal	71	66	
	Elevated	102	75	NS
β2M (mg%)	<3	36	75+	
	3.0-3.9	21	55	
	≥4	26	56	.05
IgG (mg%)	<650	41	67	
	≥650	98	61	NS
IgA (mg%)	<75	65	56	
	≥75	74	74	NS
IgM (mg%)	<30	28	54	
	≥30	111	67	NS
Marrow cellularity (clot section)	<50	36	60	
	50-84	68	67	
	≥85	57	49	NS
Marrow lymphocytes (%)	<70	43	55	
	70-89	92	74	
	≥90	34	44	.09
Cytogenetics*	Diploid	100	83	
	Other	34	53	.02
	Insufficient	27	59	

Abbreviation: NS, not significant.
*Thirteen not performed.

characteristic (shown in Table 2) was associated with the time to progression. There is no indication of a plateau developing on the curve of any group to suggest a cured fraction.

Prognostic factors for survival. Survival of patients with

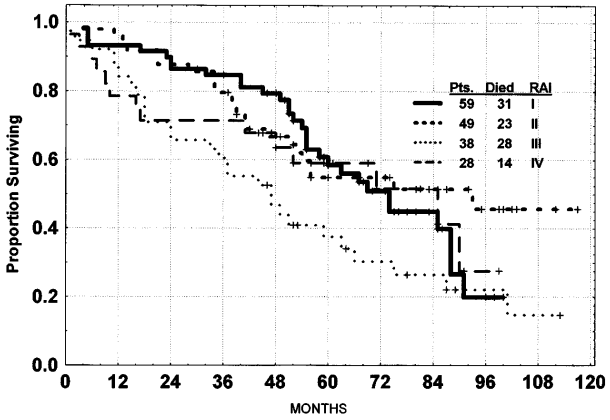
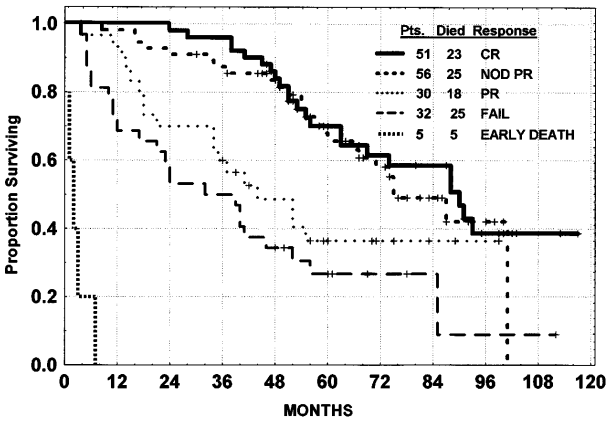


Fig 3. Survival of CLL patients treated with fludarabine by Rai stage.

survival according to whether patients had a true CR or PR-Nod (Fig 4). The survival of the CR and PR-Nod groups was signi®cantly superior to that of the PR patients ($P < .01$), who, in turn, had a signi®cantly longer survival than the resistant patients.

Rai stage was signi®cantly associated with survival. A hemoglobin level of less than 11 g% was signi®cantly associated with a shorter survival, but no such association was noted for platelet count. There was no signi®cant association of measures of tumor burden such as enlargement of liver or spleen, number of involved node sites, white blood cell count, bone marrow cellularity, or lymphocyte percentage with survival. Patients more than 70 years of age survived for a shorter time than did younger patients. The level of blood urea nitrogen in the serum was signi®cantly associated with survival, as was the serum β2-microglobulin. Cytogenetic analysis was performed on 161 patients before therapy, but 27 patients had insufficient metaphases for analysis. The 100 patients with a diploid karyotype had a signi®cant shorter survival than the aneuploid patients ($P < .01$). Abnormalities (abn) in chromosome 11q were noted in 7 patients, trisomy 12 in 7 patients, abn 13q in 3 patients, abn 14q in 6 patients, and other changes in 11 patients. The small number of patients in each group prevented



meaningful statistical analysis for response or survival. None of the other factors had a signi®cant impact on survival (Table 2).

Mortality. The survival of patients on ¯udarabine and prednisone is slightly inferior to the survival of patients on ¯udarabine as a single agent ($P = .06$; Fig 1). Ninety-six patients have died. Nine of these patients died during remission induction: 6 of infection, 1 of progressive uncontrolled CLL, 1 of cardiac failure, and 1 with a stroke. Five patients died in remission. Two patients died of pulmonary infection with unknown pathogen. One patient had a myocardial infarction. Another patient developed Hodgkin's disease and died of this disease without recurrence of the CLL. One patient died of liver cancer. Eighty-two patients died after progression of their disease or failing to respond to remission induction therapy. Thirty-®ve of these patients died of infection and 7 died of CLL, according to their local physician. Five patients died of unrelated causes, being either myocardial infarctions, cardiac arrests, or stroke. Nine patients had developed Richter's syndrome (large-cell lymphoma) at 13 to 62 months after the initiation of treatment and 8 have died. The cumulative incidence of large-cell lymphomatous transformation is projected to be 8%. In addition, 3 patients developed and died from Hodgkin's disease. Five other patients have developed cancer: 2 with lung cancer, 1 with ovarian cancer, 1 with colon cancer, and 1 with head and neck cancer. Four patients died after receiving a transplantation, 4 more died of hemorrhage, and 2 died with renal failure. No cause of death was established on follow-up in 9 patients.

Retreatment. Ninety-one patients who have come off study have received salvage therapy at MDACC. Sixty-three patients have been rechallenged with a ¯udarabine-containing regimen and 41 (67%) have responded (Table 3). For patients receiving other regimens, the response rate was 7 of 28 (25%). A number of different treatment regimens were used, as shown in Table 3. No response was noted for investigational agents such as Taxol or Topotecan. One patient achieved a PR-Nod with chlorodeoxyadenosine (2-CDA) and 2 patients responded to allogeneic bone marrow transplantation (both CRs). The CR rates were higher in patients who had achieved a true CR (11/29 [38%]) on their initial ¯udarabine treatment than for PR-Nod patients (4/30 [13%]). Seven of 16 (44%) patients who achieved a PR on their initial ¯udarabine regimen responded again when challenged, but none obtained a CR. No patient who had initially failed to respond to ¯udarabine had a response when retreated with a ¯udarabine combination. It is interesting that 4 of the 5 patients who failed to have an initial response to ¯udarabine regimens but were treated with CHOP obtained CRs (2) or PRs (2).

Immune reconstitution. Thirty-one patients had an IgG level less than 650 mg% (the lower limit of normal for our laboratory) and had at least 2 follow-up values performed to evaluate the response of the Ig level to ¯udarabine therapy. The mean of all IgG values from start of ¯udarabine until the patients commenced on another regimen was established. Of the 31 patients with a low IgG level before ¯udarabine, 12 (39%) returned to a normal level. Sixteen (51%) had an increase of more than 100 mg% from their pretreatment level and 2 patients had a decrease of 100 mg% or more from their pretreatment

Table 3. Response to Salvage Therapy in Patients Retreated After Failing or Relapsing From Fludarabine Regimens

	Fludarabine Retreatment CR + PR/Total (%)	Other Treatment CR + PR/Total (%)
Initial response		
Overall	13 + 28/63 (67)	4 + 3/28 (25)
CR	10 + 8/25 (72)	1 + 0/4 (25)
PR-Nod	3 + 13/23 (64)	1 + 1/7 (28)
PR	0 + 7/11 (70)	0/5 (Ð)
Fail	0/4 (Ð)	2 + 2/12 (33)
Time to progression (CR, PR-Nod, PR)		
<18 mo	2 + 5/11 (64)	0/8 (Ð)
18-35.9 mo	8 + 16/31 (77)	2 + 1/5 (60)
≥36 mo	3 + 7/17 (59)	0/3 (Ð)
Regimen		
Fludarabine (3 or 5 days)	8 + 18/35 (74)	
Fludara + Mitoxantrone	0 + 3/9 (33)	
FLAP	1 + 0/4 (25)	
Flud. + Ara-C + CDDP	0/2 (Ð)	
Flud. + Cyclophosphamide	4 + 7/13 (85)	
2CDA	Ð	0 + 1/2 (50)
CHOP	Ð	2 + 2/7 (57)
Chlorambucil	Ð	0/2 (Ð)
Allogeneic BMT	Ð	2 + 0/4 (50)
VP-16	Ð	0/3 (Ð)
Taxol	Ð	0/2 (Ð)
ASHAP	Ð	0/1 (Ð)
Topotecan	Ð	0/7 (Ð)

Abbreviations: CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; FLAP, fludarabine + doxorubicin + prednisone; Ara-C, cytosine arabinoside; CDDP, cis-platinum; BMT, bone marrow transplantation.

less than 75 mg%. Fourteen (26%) had a return of the IgA level to normal, 15 had an increase of 20 mg% or more (28%), and 2 (4%) had a decrease of 20 mg% or more. The other 36 patients had no substantial change. The IgM level was less than 30 mg% in 23 patients. Twelve (52%) had an increase to the normal range, 13 had an increase of 10 mg% (56%), and 1 (4%) had a decrease of more than 10 mg%. The other 9 had no substantial change. No signi®cant correlation appears to exist with the response of the patients. Patients who failed to respond had a change in their Ig levels equivalent to the CR, PR-Nod, and PR patients.

T-cell levels. Pretreatment CD4 and CD8 lymphocyte counts were available on 127 patients. The median CD4 count was 1,562/µL and the median CD8 count was 510/µL. Ninety-seven patients had CD4 and CD8 estimates after the third course and 44 patients had estimates after the sixth course of treatment (Fig 5). The median CD4 count after 3 courses was 172/µL and after 6 courses was 163/µL. The median CD8 counts after the third course and after the sixth course were 138/µL and 133/µL, respectively.

Because of concern over the low CD4 and CD8 counts, the incidence of infections that occurred while patients were in remission off treatment until they showed evidence of progressive disease or needed other treatment was examined. The

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