Fludarabine and Cytosine Arabinoside in the Treatment of Refractory or Relapsed Acute Lymphocytic Leukemia

Samer Suki, M.D., Hagop Kantarjian, M.D., Varsha Gandhi, Ph.D., Elihu Estey, M.D., Susan O'Brien, M.D., Miloslav Beran, M.D., Ph.D., Mary Beth Rios, RN., William Plunkett, Ph.D., and Michael Keating, M.B., B.S.

Background. **The objectives of the study were to evaluate the antileukemic efficacy and toxicity profiles of the combination of fludarabine and intermediate-dose cytosine arabinoside (ara-C) in refractory or relapsed adult acute lymphocytic leukemia (ALL).**

Patients and Methods. **Thirty adults with refractory or relapsed ALL were treated. Their median age was 45 years, 60% were in second or subsequent relapse, and 37% had Philadelphia chromosome-positive disease. Treatment consisted of ara-C 1 g/m^2 during a period of 2 hours daily for 6 days, and fludarabine 30 mg/m^2 during a period of 30 minutes daily for 5 days on days 2–6. Fludarabine was given 4 hours before ara-C to increase the rate of ara-C 5′-triphosphate (ara-CTP) accumulation in leukemic cells. Courses were repeated every 3 weeks or longer, depending on patient response and side effects.**

Results. **Nine (30%) patients achieved a complete remission (CR), 8 (27%) died during remission induction, and 13 (43%) had resistant disease. The median CR duration was 22 weeks, and the median survival was 12 weeks for all patients, and 34 weeks for those who had a response to treatment. Except for low platelet counts, which predicted shorter survival time, no other prognostic factors were demonstrated, considering the small number of patients treated. Myelosuppression-associated febrile episodes were the most common side effects, occurring in 28 (93%) patients. Neurotoxicity was noted in two (7%) patients.**

Conclusions. **Fludarabine and ara-C are an active and relatively safe antileukemic combination in refractory or relapsed ALL. Future studies will incorporate other anti-ALL agents, such as topoisomerase II-reactive drugs, to improve the overall efficacy, and growth factors, to reduce myelosuppression-related complications.** *Cancer* **1993; 72:2155–60.**

Key words: fludarabine, cytosine arabinoside, acute lymphocytic leukemia, salvage.

The prognosis in acute lymphocytic leukemia (ALL) has improved during the last two decades. This is attributed to advances in understanding the disease biology, improvements in remission induction and maintenance programs, and better supportive care.[1–4] With similar treatment strategies, children have higher remission and disease-free survival rates than do adults.[4–6] Currently, intensive induction and maintenance chemotherapy programs are associated with complete remission (CR) rates of 60–85% and cure rates of 25–35% in adults with ALL.[6–10] Prognostic variables that predict patient outcome include age, degree of leukocytosis, and leukemia karyotype and immunophenotype.[7–9,11] Long-term remissions are reported in 60% of adults with standard-risk ALL, and in 25% of those with poor-risk ALL.[7–9] Identification of new agents or schedules with major activity may improve patient prognosis.[12–15]

Cytosine arabinoside (ara-C), a pyrimidine analogue, is active against acute leukemia and other hematologic malignancies, such as lymphoma and myeloma. In refractory ALL, response rates of 20–65% have been reported.[16–19] Antitumor activity requires intracellular phosphorylation of ara-C into the active triphosphate form, ara-CTP, which inhibits DNA synthesis after incorporation into DNA.[20] Ara-CTP retention by leukemic cells in vitro has been correlated with remission duration[21,22] and in vivo with CR rates.[23,24] Ara-C at intermediate doses of 0.5–1 g/m^2 during a 2-hour period results in steady-state ara-C concentrations greater

From the Departments of Hematology and Medical Oncology, Division of Medicine, M. D. Anderson Cancer Center, Houston, Texas.

Supported in part by Grants CA32839 and CA57629 from the National Cancer Institute.

Address for reprints: Hagop Kantarjian, M.D., Box 61, Department of Hematology, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

Accepted for publication May 3, 1993.

than 10 μM, which saturate the ability of human leukemic cells to accumulate ara-CTP to produce maximum antitumor activity.[25]

Fludarabine (2-fluoro-ara-AMP) is a deoxyadenosine analogue. Like ara-C, fludarabine is phorphorylated to a triphosphate form (F-ara-ATP) at a rate dependent on the activity of the enzyme deoxycytidine kinase. Antileukemic activity of F-ara-ATP is, by its action, a substrate for DNA synthesis. F-ara-ATP also inhibits DNA polymerases and ribonucleotide reductase. Fludarabine initially was investigated in acute leukemia at doses of 100–150 mg/m^2 daily × 5, which produced severe neurotoxicity.[26] After establishing its acceptable tolerance and activity at lower doses of 25–30 mg/m^2 daily × 5 in chronic lymphocytic leukemia (CLL),[27] interest in its use in acute leukemia was reactivated. Evidence for the synergistic activity of fludarabine and ara-C is based on (1) the intrinsic antileukemic activity of each individually; (2) the increased ability of leukemic K562 cells and freshly isolated lymphocytes from patients with CLL to accumulate more ara-CTP after preincubation with fludarabine, possibly by increasing the activity of deoxycytidine kinase[28,29]; and (3) the results of the combination in patients with CLL[30] and with acute myelogenous leukemia (AML)[31] showing higher accumulation rates of ara-CTP and greater area under the curve of ara-CTP in leukemic cells.

This rationale was the basis for designing the current study using the sequential combination of fludarabine and ara-C in patients with refractory or relapsed ALL.

Patients and Methods

Study Population

Thirty adult patients with refractory or relapsed ALL were entered in the study after informed consent was obtained according to institutional guidelines. Criteria for entry were the presence of 30% or more blasts in the bone marrow and normal hepatic and renal functions.

Pretreatment evaluation included the following: history and physical examination; documentation of extent of disease; complete blood counts, platelet counts, and differential; SMA-12 with liver and renal function studies; bone marrow aspiration and biopsy for morphologic evaluation; and histochemical and enzymatic stains, including myeloperoxidase, periodic acid–Schiff, terminal doexynucleotidyl-transferase, and cytogenetic analysis. The diagnosis of ALL required confirmation by morphologic, cytochemical, and staining studies, i.e., positive terminal doexynucleotidyl-transferase or periodic acid–Schiff block with negative myeloid and monocytic stains. Immunophenotyping and electron microscopic studies were used for confirmatory evidence of the diagnosis.

Therapy

Induction chemotherapy consisted of ara-C 1 g/m^2 intravenously during a 2-hour period every 24 hours for six doses, and fludarabine 30 mg/m^2 intravenously during a 30-minute period for 5 days on days 2–6. Fludarabine was given 4 hours before ara-C. The first ara-C dose was given, alone as part of the pharmacologic studies to compare ara-CTP pharmacokinetics with and without exposure to fludarabine. The ara-C dose of 1 g/m^2 given during a 2-hour period has been shown to result in the accumulation of intracellular ara-CTP equal to the accumulation with a 3 g/m^2 dose.[25] The 4-hour interval between fludarabine and ara-C doses was chosen to permit maximal levels of F-ara-ATP.[29] Patients who had persistent disease received a second course of therapy 3 weeks later at the same dose schedule.

Patients experiencing CR received maintenance courses of fludarabine and ara-C for 4 days (four doses of each) every month for two to three courses, depending on patient tolerance and toxicity, followed by maintenance with 6 mercaptopurine 50 mg orally three times daily and methotrexate 20 mg/m^2 weekly.

Response Criteria

CR was defined as 5% or fewer blasts in a normocellular or hypercellular bone marrow with normal peripheral and differential counts, including a granulocyte count greater than $10^3/\mu l$ and a platelet count greater than $100 \times 10^3/\mu l$.[9] Designation as partial remission was based on similar criteria, except for presence of 6–25% marrow blasts. Patients who did not respond to induction therapy were considered to have treatment failure and were categorized as follows: (1) early death, if they died within 2 weeks after the start of therapy; (2) death during induction, if they died while receiving induction; and (3) resistant, if they survived induction therapy but experienced recurrence of leukemia.

Clinical Pharmacology

Blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after the first ara-C infusion, at 20 hours (just before fludarabine infusion), and at 20.5, 22, and 24 hours to determine ara-CTP and F-ara-ATP pharmacokinetics. On day 2, blood samples were drawn again at 24, 24.5, 25, 25.5, 26, 27, 28, 30, 32, and 34 hours to determine ara-CTP pharmacokinetics after the fludarabine infusion. Plasma was removed and mononuclear

Table 1. Patient Characteristics

Characteristic	No. of patients (%)
Age ≥ 40 yr	17 (57)
Performance status 3–4 (Zubrod)	2 (7)
Hemoglobin ≤ 10 g/dl	11 (37)
Leukocyte count > $20 \times 10^3/\mu l$	5 (17)
Platelet count < $50 \times 10^3/\mu l$	15 (50)
Peripheral blasts > 30%	9 (30)
Marrow blasts > 50%	18 (60)
Albumin < 3.5 g%	20 (67)
Lactic dehydrogenase 600 U/l	22 (73)
Duration of first remission ≤ 6 months	14 (47)
Salvage status	
First	12 (40)
Second	10 (33)
Third or more	8 (27)
Karyotype	
Philadelphia chromosome-positive	11 (37)
Diploid	8 (27)
Hyperdiploid	1 (3)
Insufficient metaphases	6 (20)
Other	4 (13)

cells were isolated by Ficoll-Hypaque density gradient centrifugation as described previously.[30] Ara-CTP and F-ara-ATP along with normal nucleotides were extracted, separated, and quantitated by high-pressure liquid chromatography.[30]

Statistical Considerations

Survival after salvage therapy was measured from the date of start of treatment and CR duration from the date of remission until documented relapse. Survival and remission duration curves were plotted by the Kaplan–Meier method.[32] Comparison of characteristics among subsets of patients was done using the chi-square or Wilcoxon tests.

Results

The characteristics of 30 patients entered in the study are detailed in Table 1. The median age was 45 years (range, 17–72 years); 19 (63%) were male patients. Fourteen (47%) patients had a first CR of less than 6 months, and 18 (60%) patients were receiving fludarabine and ara-C as their second or subsequent salvage program.

Response and Survival

Overall, 9 (30%) patients experienced CR, 8 (27%) died during remission induction, and 13 (43%) had resistant disease. Of the patients who died during remission induction, none had early death, six died of neutropenia-related infections but without evidence of leukemia, and two died with persistent leukemia. None of the eight deaths during remission induction was related to drug toxicity.

Patient response and survival by pretreatment characteristics are detailed in Table 2. There was little evidence of significant differences in response rates and survival according to pretreatment characteristics, considering the small number of patients studied. Longer survival was observed in patients with higher platelet counts ($P = 0.04$).

The median remission duration for responding patients was 22 weeks (Fig. 1). The median survival was 12 weeks for all of the patients (Fig. 1) and 34 weeks for patients experiencing treatment response.

Toxicity

Toxic effects associated with the combination treatment of fludarabine and intermediate-dose ara-C chemotherapy are detailed in Table 3. Significant nonhematologic toxicities were gastrointestinal and neurologic. Neurotoxicity was observed in two patients. One patient experienced severe motor and sensory paresis involving the lower extremities and associated with severe leg aches starting on day 35 of his first course. The neuromotor paresis had improved little by the time he died 14 weeks later. The second patient experienced peripheral neurotoxicity consisting of numbness, tingling sensations, and pain, moderate in nature, also involving the lower extremities below the knees. This started on day 34 of his first course of therapy and necessitated discontinuation of the treatment. The neurotoxicity improved gradually, becoming mild in nature by the time he died 8 months later.

Complications of myelosuppression requiring hospital admittance occurred in 28 (93%) patients. Ten patients had fever of unknown origin. Seven patients had documented bacterial infections, two with concomitant pneumonia. Fungal infection was documented in three patients, all with Candida species. Eight patients had pneumonia, three with a diffuse intermediate pattern. Multiple febrile episodes were noted in five patients.

Clinical Pharmacology

Two patients were studied for pharmacokinetic endpoints. Leukemic lymphocytes from the first patient accumulated 12 μM peak F-ara-ATP at 4 hours after fludarabine infusion. The rate of ara-CTP accumulation was 91 μM/hour during the first dose of ara-C (on day 1), whereas ara-CTP accumulation was 138 μM/hour after fludarabine infusion (on day 2), a 1.5-fold increase

Table 2. Response and Survival Time by Pretreatment Characteristics in 30 Patients

Characteristic	CR/Total (%)	*P* value	Median survival (wk)	*P* value
Total	9/30 (30)		12	
Age (yr)				
≤ 40	6/13 (46)	0.76	10	0.38
> 40	3/17 (18)		12	
Performance status (Zubrod)				
0–2	9/28 (32)	0.34	14	0.09
3–4	0/2 (0)		6	
Hemoglobin (g/dl)				
≤ 10	4/11 (36)	0.13	10	0.83
> 10	5/19 (26)		12	
Leukocyte count ($\times 10^3/\mu l$)				
≤ 5	5/13 (38)	0.53	12	0.37
> 5	4/17 (24)		10	
Platelet count ($\times 10^3/\mu l$)				
< 50	2/15 (13)	0.42	8	0.04
≥ 50	7/15 (47)		19	
Peripheral blast percent				
≤ 30	6/21 (29)	0.43	10	0.83
> 30	3/9 (33)		14	
Marrow blast (%)				
≤ 50	4/12 (33)	0.65	15	0.65
> 50	5/18 (28)		10	
Albumin (g/dl)				
≤ 3.5	8/20 (40)	0.16	10	0.60
> 3.5	1/10 (10)		15	
Lactic dehydrogenase (U/l)				
≤ 600	3/8 (38)	0.28	10	0.36
> 600	6/22 (27)		12	
Duration of first CR (mo)				
≤ 6	5/14 (36)	0.86	15	0.25
> 6	4/16 (25)		8	
Salvage status				
First	3/12 (25)		8	
Second	3/10 (30)	0.62	10	0.86
≥ Third	3/8 (38)		15	
Karyotype				
Philadelphia positive	4/11 (36)		15	
Diploid	3/8 (38)		7	
Hyperdiploid	1/1 (100)	0.29	19	0.82
Insufficient metaphases	1/6 (17)		10	
Other	0/4 (0)		8	

CR: complete response.

in the ara-CTP accumulation after fludarabine infusion. In the second patient, the rates of ara-CTP accumulation in leukemic cells remained similar before (122 μM/hour, day 1) and after fludarabine (114 μM/hour, day 2) infusions. The peak level of F-ara-ATP at the time of second ara-C infusion was only 6 μM. The plasma ara-C concentrations, the levels of its deamination product arabinosyluracil, and the rate of ara-CTP elimination from the leukemic lymphocytes were not affected by fludarabine infusion. Thus, the increase in the rate of ara-CTP accumulation was the factor responsible for the augmentation of ara-CTP area under the curve in these cells.

Discussion

The combination of fludarabine and ara-C has demonstrated encouraging antileukemic efficacy in patients

with AML in salvage[33] and in front-line induction chemotherapy.[34] In adult ALL, combination regimens including high-dose ara-C and asparaginase, mitoxantrone, or amsacrine[35–39] generally have shown higher response rates than have those with high-dose ara-C alone.[37]

This is the first study combining fludarabine and intermediate-dose ara-C in the treatment of refractory ALL. Overall, 9 of 30 (30%) patients experienced CR. The induction mortality of 27% was significant and may be reduced by the incorporation of growth factors as adjunctive supportive therapy.[40] Because of the small number of patients treated, and the lack of obvious prognostic factors, it is difficult to ascertain whether the addition of fludarabine had any significant antileukemic contribution. This also is complicated by the absence of any studies using single-agent fludarabine at the current dose schedule and the confinement of the antileukemic efficacy of single-agent fludarabine to dose-schedules producing prohibitive neurotoxicity (100–150 mg/m^2 daily × 5).[26] Thus, although the current study has established the safety and overall efficacy of the combination regimen in refractory adult ALL, additional studies are needed to determine the individual contribution of fludarabine to the overall antileukemic activity. If established, the introduction of the combination into front-line therapy as part of alternating non–cross-resistant regimens may improve the overall cure fraction in adult ALL, especially among patients with poor prognosis.

The combination of fludarabine and intermediate-dose ara-C was well tolerated. Nonhematologic toxicities were acceptable. However, myelosuppression-associated problems were significant, with febrile episodes observed in 93% of patients. This incidence is similar to that seen in previous intensive combination regimens in ALL salvage[35–39] and may be ameliorated by the addition of growth factors, which would allow a safer use of the regimen in front-line ALL maintenance therapy. Despite the potential neurotoxicity of each agent, the neurotoxicity of the combination was acceptable. Interstitial pneumonitis, noted in three patients, was attributed to infections, rather than fludarabine-associated pulmonary toxicity.

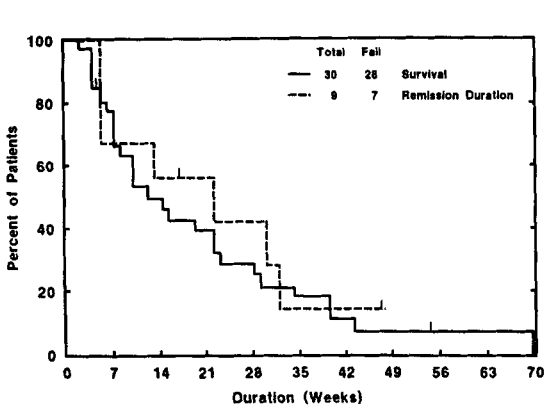

Figure 1. Remission duration and survival of patients with refractory ALL treated with fludarabine and intermediate-dose cytosine arabinoside.

Table 3. Side Effects of the Combination Treatment

Toxicity	No. of patients (%)
Nausea and vomiting	3 (10)
Moderate to severe diarrhea	3 (10)
Severe mucositis	1 (3)
Neurotoxicity	2 (7)
Pericarditis	1 (3)
Conjunctivitis	2 (7)
Febrile episodes	
Fever of unknown origin	10 (33)
Bacterial	7 (23)
Fungal	3 (10)
Pneumonia	8 (27)

Because fludarabine infusion before ara-C therapy demonstrated potentiation of the ara-CTP area under the curve in circulating leukemia cells of patients with CLL[30] and AML,[31] the pharmacokinetic objective in the current study was to determine if similar augmentation could be achieved in patients with ALL. Pharmacokinetic data from one patient indicated that similar levels of augmentation for the rate of ara-CTP accumulation could be achieved in lymphoblasts, as observed in patients with CLL (1.3-fold[30]) and AML (1.8-fold[31]). The levels of F-ara-ATP at the time of ara-C infusion were 12 μM in our patient, the median value being 16 μM in patients with CLL (n = 8) and 20 μM in patients with AML (n = 10). The second patient with ALL, whose cells accumulated only a 6-μM peak F-ara-ATP level, did not augment the rate of ara-CTP accumulation. These data may suggest that more than 10 μM of intracellular F-ara-ATP are needed for activation of anabolism of ara-C, but the number of patients analyzed was too small to make any definite conclusions.

References

1. Rivera G, Raimondi S, Hancock M, et al. Improved outcome in childhood acute lymphocytic leukemia with reinforced early treatment and rotational combinations. *Lancet* 1991; 337:61–6.
2. Clavell LA, Gleker RD, Cohen HJ, et al. Four-agent induction and intensive asparginase therapy for treatment of childhood acute lymphoblastic leukemia. *N Engl J Med* 1986; 315:657–63.
3. Rivera GK, Mauer AM. Controversies in the management of childhood acute lymphoblastic leukemia: treatment intensifica-

tion, CNS leukemia, and prognostic factors. *Semin Hematol* 1987; 24:12–26.
4. Gree JS, Haghbin M, Dowling MD Jr., et al. Acute lymphoblastic leukemia in adults and children. *Cancer* 1976; 37:1256–64.
5. Sackaman-Muriel F, Savarch E, Eppinger-Helft M, et al. Evaluation of intensification and maintenance programs in the treatment of acute lymphoblastic leukemia. *Cancer* 1978; 42:1730–40.
6. Clarkson B, Ellis S, Little C, et al. Acute lymphoblastic leukemia in adults. *Semin Oncol* 1985; 12:160–79.
7. Gaynor J, Chapman D, Little C, et al. A course-specific hazard rate analysis of prognostic factors among 199 adults with acute lymphoblastic leukemia: the Memorial Hospital experience since 1969. *J Clin Oncol* 1988; 6:1014–30.
8. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 1988; 71:123–33.
9. Kantarjian HM, Walters RS, Keating MJ, et al. Results of the vincristine, doxorubicin and dexamethasone regimen in adults with standard- and high-risk acute lymphocyte leukemia. *J Clin Oncol* 1990; 9:994–1004.
10. Linker CA, Levitt LJ, O'Donnell M, et al. Improved results of treatment of adult acute lymphoblastic leukemia. *Blood* 1987; 69:1242–8.
11. Third International Workshop on Chromosomes in Leukemia. Chromosomal abnormalities and their clinical reference in acute lymphocytic leukemia. *Cancer Res* 1983; 43:868–73.
12. Abromowitch M, Bowman WP, Ochs J, Rivera G. Etoposide (VP-16) with prednisone and vincristine for the treatment of refractory acute lymphoblastic leukemia. *J Clin Oncol* 1985; 3:789–92.
13. Rivera G, Dahl GV, Bowman WP, et al. VM-26 and cytosine arabinoside combination chemotherapy for initial induction failures in childhood lymphocytic leukemia. *Cancer* 1980; 46:1727–30.
14. Bostrom B, Woods G, Nesbit E, et al. Successful reinduction of patients with acute lymphoblastic leukemia who relapse following bone marrow transplantation. *J Clin Oncol* 1987; 5:376–81.
15. Ryan DH, Kopecky KJ, Gumbart CH, et al. Southwest Oncology Group Trial: VM-26 and ifosfamide in refractory adult lymphocytic leukemia [abstract]. *Proc Am Soc Clin Oncol* 1987; 6:143.
16. Kantarjian HM, Estey EH, Plunkett W, et al. Phase I-II clinical and pharmacologic studies of high-dose cytosine arobinoside in refractory leukemia. *Am J Med* 1986; 81:387–94.
17. Capizzi RL, Poole M, Cooper MR, et al. Treatment of poor risk acute leukemia with sequential high-dose ara-C and asparaginase. *Blood* 1984; 63:694–700.
18. Herzig RH, Wolff SN, Lazarus HM, et al. High-dose cytosine arabinoside therapy for refractory leukemia. *Blood* 1983; 62:361–5.
19. Peters WG, Cathy LP, Willemze R. High-dose cytosine arabinoside-pharmacological and clinical aspects. *Blut* 1988; 56:1–11.
20. Kufe D, Major P, Egan E, et al. Correlation of cytotoxicity with incorporation of ara-C into DNA. *J Biol Chem* 1980; 255:8997–9000.
21. Rustum YM, Preisler HD. Correlation between leukemic cell retention of 1-B-D arabinofuranosylcytosine 5'-triphosphate and response to therapy. *Cancer Res* 1970; 39:42–3.
22. Preisler HD, Rustum YM, Priore RL. Relationship between leukemic cell retention of cytosine arabinoside triphosphate and duration of remission in patients with acute non-lymphocytic leukemia. *Eur J Cancer Clin Oncol* 1985; 21:23–9.
23. Plunkett W, Iacoboni S, Estey EH, et al. Pharmocologically directed ara-C therapy for refractory leukemia. *Semin Oncol* 1985; 12(Suppl 3):20–30.
24. Estey E, Plunkett W, Dixon D, et al. Variables predicting response to high dose cytosine arabinoside therapy in patients with refractory acute leukemia. *Leukemia* 1987; 1:580–3.
25. Plunkett W, Liliemark JO, Adams TM, et al. Saturation of 1-β-D-arabinofuranosylcytosine 5'-triphosphate accumulation in leukemia cells during high-dose 1-β-D-arabinofuranosyl cytosine therapy. *Cancer Res* 1987; 97:3005–11.
26. Warrell RP, Berman E. Phase I and II study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity. *J Clin Oncol* 1986; 4:74–9.
27. Keating MJ, Kantarjian HM, O'Brien S, et al. Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. *J Clin Oncol* 1989; 7:1071–80.
28. Gandhi V, Plunkett W. Modulation of arabinosyl nucleoside metabolism by arabinosyl nucleotides in human leukemia cells. *Cancer Res* 1988; 48:329–34.
29. Gandhi V, Nowak B, Keating MJ, et al. Modulation of arabinosyl-cytosine metabolism by arabinosyl-2-fluoroadenine in lymphocytes from patients with chronic lymphocytic leukemia: implications for combination chemotherapy. *Blood* 1989; 74: 2070–5.
30. Gandhi V, Kemena A, Keating MJ, et al. Fludarabine potentiates arabinosyl-cytosine metabolism in lymphocytes of patients with chronic lymphocytic leukemia. *Cancer Res* 1992; 52:897–903.
31. Gandhi V, Estey E, Keating MJ, et al. Fludarabine potentiates metabolism of arabinosylcytosine in patients with acute myelogenous leukemia during therapy. *J Clin Oncol* 1993; 11:116–24.
32. Kaplan ES, Meier P. Nonparametric estimations from incomplete observations. *Am Stat Assoc* 1958; 53:457–81.
33. Estey E, Plunkett W, Gandhi V, Rios M, Kantarjian H, Keating M. Fludarabine and arabinosyl cytosine therapy of refractory and relapsed acute myelogenous leukemia. *Leukemia Lymphoma* 1993; 9:343–50.
34. Estey E, Kantarjian H, O'Brien S, et al. Treatment of poor prognosis newly diagnosed AML or MDS with G-CSF prior to, during and following fludarabine and ara-C (FLAG). *Blood* 1992; 80:112a.
35. Wells RJ, Fensner J, Devney R, et al. Sequential high-dose cytosine arabinoside-asparaginase treatment in advanced childhood leukemia. *J Clin Oncol* 1985; 3:998–1004.
36. Hiddemann M, Kreutzman H, Straif K, et al. High-dose cytosine arabinoside in combination with mitoxontrone for the treatment of refractory acute myeloid and lymphoblastic leukemia. *Semin Oncol* 1987; 14:73–7.
37. Kantarjian HM, Walters RL, Keating MJ, et al. Mitoxantrone and high-dose cytosine arabinoside for the treatment of refractory acute lymphocytic leukemia. *Cancer* 1990; 65:5–8.
38. Ishii E, Mann T, Ohkubi K, et al. Treatment of childhood acute lymphoblastic leukemia with intermediate dose cytosine arabinoside and Adriamycin. *Med Pediatr Oncol* 1986; 14:73–7.
39. Arlin Z, Feldman E, Kempin S, et al. Amasacrine with high-dose cytarabine is highly effective therapy for refractory and relapsed acute lymphoblastic leukemia in adults. *Blood* 1988; 72:433–5.
40. Kantarjian HM, Estey EH, O'Brien S, Anaissie E, Beran M, Rios M-B, et al. Intensive chemotherapy with mitoxantrone and high-dose cytosine arabinoside followed by granulocyte-macrophage colony-stimulating factor in the treatment of patients with acute lymphocyte leukemia. *Blood* 1992; 79:876–81.