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Clinical pharmacology of cytarabine in patients with acute myeloid leukemia: a Cancer and Leukemia Group B study

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Abstract The pharmacokinetics of cytarabine (ara-C) were determined in 265 patients with acute myeloid leukemia (AML) receiving ara-C (200 mg/m^2 per day for 7 days as a continuous infusion) and daunorubicin during induction therapy. The mean (standard deviation) ara-C concentration at steady-state (Css) and systemic clearance (Cl) were 0.30 (0.13) μ*M* and 134 (71) l/h per m^2 respectively. Males had a significantly faster ara-C Cl (139 vs 131 l/h per m^2, $P = 0.025$) than females. Significant correlations were noted between ara-C Cl and the pretreatment, peripheral white blood cell count ($P = 0.005$) and pretreatment blast count ($P = 0.020$). No significant differences in ara-C Css or Cl were noted in patients achieving complete remission compared with those failing therapy ($P = 0.315$, $P = 0.344$, respectively). No significant correlations were observed between ara-C pharmacokinetic parameters and several indices of patient toxicity. Our findings indicate that variability in ara-C disposition in plasma at this dosage level does not correlate with remission status or toxicity in patients with AML receiving initial induction therapy with ara-C and daunorubicin.

Key words Cytarabine · Leukemia

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Introduction

The antimetabolite 1-β-D-arabinofuranosylcytosine (ara-C) is one of the most effective agents in the treatment of acute myeloid leukemia (AML). When ara-C is administered by continuous infusion (200 mg/m^2 per day for 7 days) in combination with an anthracycline, approximately 65% of patients with AML achieve complete remission (CR) [9]. However, most patients achieving CR eventually relapse. The pharmacologic and biochemical factors which contribute to treatment response or failure have not yet been clearly defined.

Although biochemical interactions at the cellular level are critical in determining tumor sensitivity to anticancer drug therapy, interpatient variability in the pharmacokinetics of anticancer drugs may contribute to their efficacy or toxicity. The systemic clearance of several anticancer agents can vary 2–10-fold among patients with cancer [10]. In the treatment of childhood acute leukemia, interpatient variability in the

disposition of anticancer agents has been correlated with antileukemic response. Specifically, children with a rapid systemic clearance of methotrexate [11] or mercaptopurine [13, 15] have a higher probability of relapse during post-remission therapy than children with a slower systemic clearance.

The relationships between ara-C disposition in plasma and patient outcome have not been fully evaluated. Previous studies [1, 25] have not identified relationships between ara-C plasma pharmacokinetics and indices of response. However, these studies were limited by small sample sizes. The objectives of this multicenter investigation were the following: (1) to describe the systemic disposition of ara-C in a large population of patients with AML, (2) to determine factors which account for interpatient pharmacokinetic variability of ara-C, and (3) to evaluate correlations between ara-C pharmacokinetics and various indices of leukemic response and host toxicity.

Materials and methods

Treatment protocol and patient population

Between 1985 and 1990, 342 patients were evaluated in this clinical pharmacologic study. This study was performed in conjunction with a Cancer and Leukemia Group B multicenter trial (CALGB 8525) evaluating the effect of different doses and schedules of ara-C administered during post-remission therapy on survival and toxicity in patients with *de novo* AML [18]. All patients provided signed informed consent before entry on both the treatment and clinical pharmacology protocols. Prior to study entry, a bone marrow aspirate was obtained and examined to confirm the diagnosis of AML. Eligible patients were required to have satisfactory hepatic and renal function (total bilirubin < 3.0 mg/dl; alkaline phosphatase, SGOT, SGPT $< 2 \times$ normal; serum creatinine < 2.0 mg/dl). All patients received an induction regimen consisting of daunorubicin 45 mg/m^2 per day, days 1–3, and ara-C 200 mg/m^2 per day by continuous intravenous infusion, days 1–7. In patients > 60 years old, the daunorubicin dose was reduced to 30 mg/m^2 per day, days 1–3. On day 14, a repeat bone marrow examination was performed and the antileukemic effect of therapy was determined. Patients failing to achieve CR could receive a second induction course consisting of the same dose of daunorubicin (days 1–2) and ara-C (days 1–5). Patients achieving CR were then randomized to receive one of three ara-C doses for post-remission therapy. Only the clinical pharmacologic findings during induction therapy are presented in this report.

Evaluation of response and toxicity

CR following induction therapy was defined as $< 5\%$ blasts on bone marrow examination with normal marrow cellularity and a return to normal peripheral blood counts. Patients not achieving CR (NR) were defined as having one of the following responses: partial remission, death with leukemic marrow, death with aplastic marrow, or death with unknown marrow. Patients were evaluated for toxicities to major organ systems during induction therapy and the toxicites were graded from 0 (no toxicity) to 5 (lethal) using the National Cancer Institute Common Toxicity Criteria [12].

Sample collection

Prior to ara-C administration and on days 1, 3, and 6 during the initial ara-C infusion, 5 ml of blood was collected in cooled, heparinized tubes containing the cytidine deaminase inhibitor tetrahydrouridine (0.5 mg). In patients receiving a second induction course, blood samples were collected prior to and on days 1, 3, and 5 of the ara-C infusion. The protocol specified that blood samples were not to be collected from the central venous catheter (the site of the ara-C infusion) but rather from a peripheral site. After blood collection, the samples were immediately centrifuged (2000 g, 4° C, 10 min) and the plasma transferred into tubes. Plasma samples were frozen ($-20°$ C) and shipped on dry ice to the Upjohn Co. (Kalamazoo, Mich.) for determination of ara-C concentrations. The concentration of ara-C in plasma was determined by a specific radioimmunoassay technique [20]. The sensitivity of this method for ara-C was 1 ng/ml with a cross-reactivity with uracil arabinoside of 0.008%. This method has been shown previously to yield similar results to HPLC [3].

Pharmacokinetic analysis

The ara-C concentration at steady-state (Css) during each induction-course was calculated by averaging the plasma ara-C concentrations during the ara-C infusion. Since the ara-C elimination half-life is significantly shorter than the length of the ara-C infusion, ara-C systemic clearance (Cl) was calculated from the following equation:

$$\mathrm{Cl} = \frac{\mathrm{K_0}}{\mathrm{Css}}$$

where K_0 is the ara-C infusion rate and Css is the ara-C concentration at steady-state. Because the length of infusion varied slightly among patients, ara-C Cl was calculated based upon each patient's actual infusion rate.

In patients having pharmacokinetic data from two induction courses, the mean ara-C Css and Cl of the two courses were used in certain analyses. The effect of certain variables (e.g. gender, cytogenetics, etc.) on the disposition of ara-C was determined by first separating each variable into two groups (e.g. males and females) and comparing the ara-C Css and Cl between groups. Patients with the following cytogenetic findings: t(8; 21), t(15; 17), rearrangements involving 16q22, or normal karyotype were classified as having a "favorable" prognosis, while patients with other cytogenetic findings were classified as "other."

Statistical and pharmacodynamic analysis

The means of demographic, histologic, pharmacologic, and other laboratory data were determined along with the standard deviation (SD). Correlations between the ara-C pharmacokinetics between the first and second induction course were estimated nonparametrically with the Spearman rank correlation coefficient [24]. Comparison of ara-C pharmacokinetics between groups of patients was tested nonparametrically for statistical significance and stratified by the number of induction courses (one or two) [7]. The relationship between ara-C pharmacokinetics and response was also tested for statistical significance, adjusting for the number of induction courses.

We applied a variety of regression techniques (linear, logistic, and proportional hazards) to model relationships with multiple covariates and ara-C pharmacokinetic parameters. Because these adjusted multivariate analyses did not produce different results from the simple analyses, only the simple analyses are presented. Linear regression [14] analysis was used to model the association between the logarithm of ara-C Cl during the first induction course and either the logarithm of the pretreatment total white blood cell count or the

logarithm of the total peripheral blast count. Logistic regression [6] was used to model the association between ara-C Css or Cl and toxicity. Associations between ara-C disposition and specific toxicities (frequency of nausea and vomiting, infection, stomatitis, diarrhea, anemia, thrombocytopenia) were tested nonparametrically, using the same methods (adjusted for the number of induction courses) used for comparing ara-C pharmacokinetics between groups [7].

All quoted *P*-values are two-sided with the *a priori* level of significance set at $P = 0.05$. No adjustment for multiple comparisons was made.

Results

Pharmacokinetic data were obtained from 342 patients. Because this pharmacokinetic trial was conducted at multiple institutions, strict guidelines were developed concerning the infusion of ara-C, blood collection, and processing of blood samples. It was necessary to exclude 77 patients from analysis for the following reasons: 39 patients had samples obtained from a central venous catheter used for the infusion of ara-C; in 10 patients the duration of the ara-C infusion was either significantly shortened (> 6 h less than the recommended infusion duration) or lengthened (> 12 h longer than the recommended infusion duration); 7 patients had multiple interruptions of their ara-C infusion; 7 patients died during the infusion; 6 patients had pretreatment samples but no samples obtained during the ara-C infusion; 5 patients had samples that were unsuitable for assay; 2 patients withdrew from the study; and 1 patient was given the wrong dose.

Thus, 265 patients were evaluable for pharmacokinetic and pharmacodynamic analysis. Of these, 227 patients had pharmacokinetic data only for the first course, 6 had pharmacokinetic data only for the second course, and 32 had data for both courses representing 297 total courses of therapy. The characteristics of the patient population are summarized in Table 1.

Examination of bone marrow aspirates obtained prior to drug therapy revealed that 88% of patients had either hypercellular or packed bone marrows. According to cytogenetic analysis of bone marrow samples from 197 patients, 60% of patients had cytogenetic findings that were associated with a "favorable" prognosis. Following induction therapy, CR was achieved in 62% of the 265 patients evaluable for analysis.

Table 1 Patient Characteristics

No. of patients	265
Age (years; median, range)	49 (17–79)
Sex	
Male	134 (51%)
Female	131 (49%)
Race	
White	229 (86%)
Black	27 (10%)
Other	9 (4%)
Performance status ($n = 263$)	
0	81 (31%)
1	124 (47%)
2	36 (14%)
3	17 (6%)
4	5 (2%)
FAB classification	
M1	54 (20.4)
M2	83 (31.3)
M3	25 (9.4)
M4	66 (24.9)
M5	28 (10.6)
M6	4 (1.5)
Other	5 (1.9)
Cytogenetics ($n = 197$)	
Favorable	119 (60.4)
Other	78 (39.6)

Table 2 Summary of ara-C pharmacokinetics during induction therapy. Values are means (SD). In patients having data from course 1 and 2, the average of both courses was used

	Ara-C Css (μM)	Cl (l/h per m^2)
First induction ($n = 259$)	0.31 (0.13)	132 (68)
	0.05–1.09	30–703
First quartile	0.22	94
Third quartile	0.36	155
Second induction ($n = 38$)	0.29 (0.12)	153 (104)
	0.07–0.60	60–507
First quartile	0.20	95
Third quartile	0.36	173
Combined ($n = 265$)	0.30 (0.12)	135 (71)
	0.05–1.09	30–703
First quartile	0.22	95
Third quartile	0.36	156

Pharmacokinetics

Significant interpatient variability in ara-C Css and Cl was observed during induction therapy (Table 2). The frequency distribution of ara-C Cl from data during the first induction cycle is shown in Fig. 1. In 32 patients having ara-C pharmacokinetic data obtained during the first and second induction courses, no significant difference was observed between the first and second induction courses in either ara-C Css ($P = 0.4087$) or ara-C Cl ($P = 0.5580$).

Because of the wide variability in ara-C disposition, the effect of various demographic and laboratory variables on ara-C Css and Cl was examined, adjusting for the number of induction courses. A summary of these analyses is shown in Table 3. Race did not have a significant effect on the disposition of ara-C with ara-C Css and Cl not significantly different between whites and nonwhites ($P = 0.927$ and 0.955, respectively).

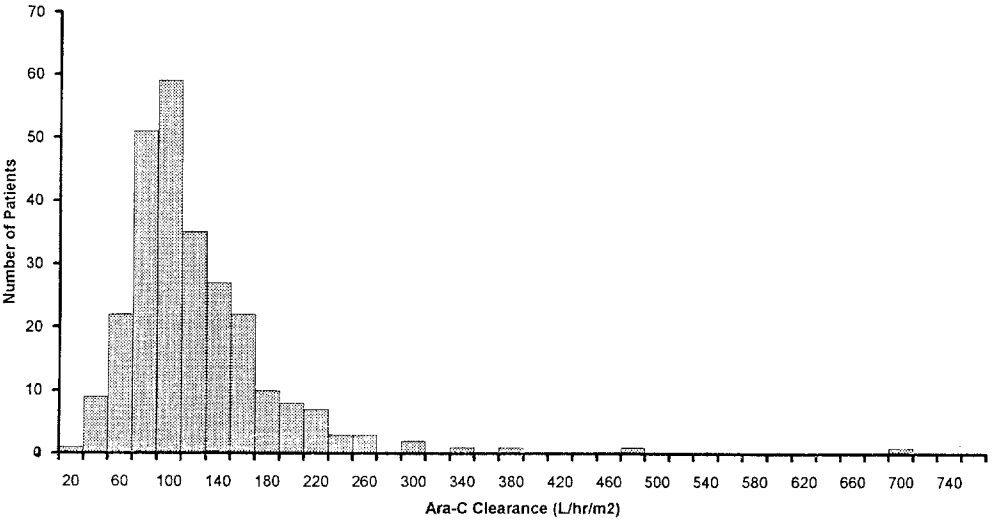

Fig. 1 Frequency distribution of ara-C plasma clearance in patients receiving ara-C 200 mg/m^2 per day by continuous intravenous infusion during the first course of induction therapy

Table 3 Demographic and response variables and ara-C disposition. Values are means (SD) (*CR* complete remission, *NR* no response)

Variable	Ara-C Css (μM)	*P*-value	Ara-C Cl (1/h per m^2)	*P*-value
Age (years)				
≤ 60 ($n = 173$)	0.30 (0.11)		135 (63)	
> 60 ($n = 92$)	0.32 (0.13)	0.070	132 (85)	0.098
Sex				
Males ($n = 136$)	0.30 (0.13)		139 (71)	
Females ($n = 129$)	0.31 (0.11)	0.022	131 (71)	0.025
Response to therapy				
CR ($n = 164$)	0.29 (0.11)		138 (74)	
NR ($n = 101$)	0.32 (0.14)	0.315	125 (54)	0.344

A significant positive correlation was noted between induction 1 ara-C Cl and the pretreatment peripheral white blood cell count ($P = 0.005$, $R^2 = 0.034$) such that a high white blood cell count was associated with a fast ara-C Cl. A significant correlation was also noted between the induction 1 ara-C Cl and the pretreatment, peripheral blast count ($P = 0.020$, $R^2 = 0.024$). Ara-C Css or Cl was not significantly different in patients having "favorable" cytogenetic characteristics and in patients having "other" findings ($P = 0.45$ and 0.54, respectively).

Pharmacodynamics

Because of the wide interpatient variability in ara-C Css and Cl, ara-C pharmacokinetic parameters between patients achieving CR and NR patients were compared. Neither ara-C Css ($P = 0.32$) nor Cl ($P = 0.34$) were significantly different in patients achieving CR ($n = 164$) and in NR patients ($n = 101$). These analyses were repeated in the group of patients receiving only one induction course and again no significant differences between patients achieving CR and NR patients were observed for ara-C Css ($P = 0.88$) or Cl ($P = 0.99$). In an analysis restricted to patients with "favorable" cytogenetic findings, no significant differences were observed between patients achieving CR and NR patients in ara-C Css ($P = 0.447$) or ara-C Cl ($P = 0.543$).

Correlations between specific, individual patient toxicities (i.e. frequency of nausea and vomiting, infection, stomatitis, diarrhea, anemia, thrombocytopenia) and ara-C pharmacokinetics were assessed. Of the analyses performed, only the relationship between ara-C Cl in patients receiving only one induction course and stomatitis of grade 2 or higher (i.e. slow Cl, increased stomatitis) approached statistical significance ($P = 0.054$).

Discussion

This trial provides the first information concerning the clinical pharmacology of ara-C (200 mg/m^2 per day) in a large population of patients with AML. In this multicenter investigation of the pharmacokinetics and

pharmacodynamics of standard dose ara-C during induction therapy for AML, significant interpatient variability in the disposition of ara-C was noted. Several factors contributing to the interpatient variability in ara-C pharmacokinetics were observed.

The pharmacokinetics of several drugs, including anticancer compounds have been demonstrated to be altered in the elderly. Differences in ara-C Cl in patients > 60 years old and in younger patients approached statistical significance. A number of physiologic factors, including the activity of enzymes responsible for drug metabolism, are diminished in the elderly [5, 8]. Whether advancing age is associated with a decline in cytidine deaminase activity is not known.

Males had a significantly faster ara-C Cl than females. This observation is probably of little clinical significance given the small difference noted (139 vs 131 l/h per m^2). Gender-related differences in drug disposition have been reported for several drugs [2], including anticancer agents [19].

Interestingly, we noted a significant relationship between disease burden and ara-C Cl. Specifically, patients with higher pretreatment white cell or blast counts had a faster ara-C Cl. Leukemic blasts have been noted to have significant cytidine deaminase activity [17]. An increased burden of leukemic cells may accelerate the degradation of ara-C and influence the cytotoxic response to ara-C [17].

Despite wide interpatient variability in ara-C Css and Cl, no significant differences in ara-C Css or Cl between patients achieving CR versus NR patients were noted. The concomitant administration of daunorubicin may have obscured any potential associations between ara-C disposition and host response and/or toxicity. Several discoveries concerning ara-C pharmacology described below, may explain why interpatient pharmacokinetic variability at this ara-C dose was not correlated with remission status.

Ara-C is transported into leukemia cells by a facilitated diffusion process utilized by nucleosides [21]. Once within the cell, ara-C is phosphorylated in three successive steps into the 5'-triphosphate, ara-CTP. Ara-CTP has multiple effects on DNA synthesis including inhibition of DNA polymerase α, incorporation into DNA, and termination of DNA chain elongation. The extent and rate of formation of ara-CTP is correlated with cytotoxicity. Studies conducted by other investigators during the conduct of our investigation have indicated that there is no relationship between plasma ara-C Css and intracellular concentrations of ara-CTP in leukemic blasts [16, 23].

The lack of correlation between plasma ara-C concentrations and intracellular ara-CTP concentrations can be accounted for by the biochemical factors influencing ara-CTP formation. Leukemic blasts obtained from patients have significantly fewer nucleoside binding sites, as measured by the nitrobenzyl mercaptopurine riboside (NBMPR) binding sites, than human or murine cell lines [26–29]. This discrepancy in nucleoside binding sites results in substantially lower ara-C transport rates in patient blasts than in experimental cell lines. Although transport rates are generally lower in patient blasts, the rate of transport can differ significantly between patients. These observations indicate that with standard dose ara-C regimens, transport may be rate-limiting and ara-C is phosphorylated as rapidly as it enters the cells.

The importance of extracellular ara-C concentration on transport can be determined by calculations of ara-C control strength which incorporate extracellular ara-C concentrations and kinetic constants for transport and intracellular phosphorylation [30]. At concentrations achieved during standard dose therapy (e.g. 0.30 μM), transport is calculated to be the rate-limiting factor using median patient data. These calculations indicate that limitations in transport can be overcome by elevating ara-C concentrations to 10–15 μM [4]. However, studies have indicated that the formation of ara-CTP is saturable at concentrations in excess of 10 μM [22]. Plasma ara-C concentrations obtained from current high-dose ara-C regimens (≥ 50 μM) are in considerable excess of the concentrations necessary to saturate ara-CTP formation and may increase the risk of severe toxicity.

In conclusion, despite wide interpatient variability in ara-C pharmacokinetics during induction therapy, no relationship between remission status and ara-C disposition was noted. As indicated above, interpatient variability in methotrexate [11] and mercaptopurine [13, 15] pharmacokinetics has been correlated with remission status in childhood leukemia. However those studies involved pharmacokinetic investigations during post-remission therapy. The clinical impact of interpatient variability of ara-C pharmacokinetics during post-remission therapy is currently being investigated by the Cancer and Leukemia Group B.

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References

1. Avramis VI, Biener R, Krailo M, et al (1987) Biochemical pharmacology of high dose 1-ß-D-arabinofuranosylcytosine in childhood acute leukemia. Cancer Res 47: 6786
2. Bonate PL (1991) Gender-related differences in xenobiotic metabolism. J Clin Pharmacol 31: 684
3. Capizzi RL, Yang JL, Cheng E, et al (1983) Alteration of the pharmacokinetics of high-dose ara-C by its metabolite, high ara-U in patients with acute leukemia. J Clin Oncol 1: 763
4. Capizzi RL, White JC, Powell BL, Perrino F (1991) Effect of dose on the pharmacokinetic and pharmacodynamic effects of ara-C. Semin Hematol 28 [Suppl 4]: 54
5. Cohen J (1986) Pharmacokinetic changes in aging. Am J Med 80 [Suppl 5A]: 31

6. Cox DR (1970) Analysis of binary data. Chapman and Hall, London
7. Cuzik J (1985) A Wilcoxon-type test for trend. Stat Med 4: 87
8. Dawling S, Crome P (1989) Clinical pharmacokinetic considerations in the elderly. An update. Clin Pharmacokinet 17: 236
9. Dillman RO, Davis RB, Green MR, et al (1991) A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. Blood 78: 2520
10. Evans WE and Relling MV (1989) Clinical pharmacokinetics-pharmacodynamics of anticancer drugs. Clin Pharmacokinet 16: 327
11. Evans WE, Crom WR, Abromowitch M, et al (1986) Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia: identification of a concentration-effect relationship. N Engl J Med 314: 471
12. Green S, Weiss GR (1992) Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10: 239
13. Hayder S, Lafolie P, Bjork O, Peterson C (1989) 6-mercaptopurine plasma levels in children with acute lymphoblastic leukemia: relation to relapse risk and myelotoxicity. Ther Drug Monit 11: 617
14. Kleinbaum DG, Kupper LL, Muller KE (1988) Applied regression analysis and other multivariate methods (2nd edn.) PWS-Kent, Boston
15. Koren G, Ferrazini G, Sulh H, et al (1990) Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. N Engl J Med 323: 17
16. Liliemark JO, Plunkett W, Dixon DO (1985) Relationship of 1-β-D-arabinofuranosylcytosine in plasma to 1-β-D-arabinofuranosylcytosine 5-triphosphate levels in leukemic cells during treatment with high-dose 1-ß-D-arabinofuranosylcytosine. Cancer Res 45: 5952
17. Mancini WR (1992) The role of deoxycytidine-metabolizing enzymes in the cytotoxicity induced by 3'-amino-2',3'-dideoxycytidine and cytosine arabinoside. Cancer Chemother Pharmacol 30: 139
18. Mayer RJ, Davis RB, Schiffer CA, et al (1994) Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 331: 896
19. Milano G, Etienne MC, Cassuto-Viguier E, et al (1992) Influence of sex and age on fluorouracil clearance. J Clin Oncol 10: 1171
20. Piall EM, Aherne GW, Marks VM (1979) Radioimmunoassay for cytosine arabinoside. Br J Cancer 40: 548
21. Plagemann PGW, Marz R, Wohlhueter RM (1978) Transport and metabolism of deoxycytidine and 1-ß-D-arabinofuranosylcytosine into cultured Novikoff rat hepatoma cells, relationship to phosphorylation, and regulation of triphosphate synthesis. Cancer Res 38: 978
22. Plunkett W, Lilliemark JO, Adams TM et al (1987) Saturation of 1-β-arabinofuranosylcytosine 5'-triphosphate accumulation in leukemia cells during high dose 1-ß-D-arabinosylcytosine therapy. Cancer Res 47: 3005
23. Riva CM, Rustum YM, Preisler HD (1985) Pharmacokinetics and cellular determinants of response to 1-ß-arabinofuranosylcytosine (ara-C). Semin Oncol 12 [Suppl 3]: 1
24. Rosner B (1990) Fundamentals of biostatistics. PWS-Kent, Boston
25. Rustum YM, Riva C, Priesler HD (1987) Pharmacokinetic parameters of 1-β-D-arabinofurannosylcytosine (ara-C) and their relationship to intracellular metabolism of ara-C, toxicity, and response of patients with acute nonlymphocytic leukemia treated with conventional and high-dose ara-C. Semin Oncol 14 [Suppl 1]: 141
26. White JC, Rathmel JP, Capizzi RL (1987) Membrane transport influences the rate of accumulation of cytosine arabinoside in human leukemia cells. J Clin Invest 79: 380
27. Wiley JS, Jones SP, Sawyer WH (1982) Cytosine arabinoside influx and nucleoside transport sites in acute leukemia. J Clin Invest 69: 479
28. Wiley JS, Jones SP, Sawyer WH (1983) Cytosine arabinoside transport by human leukemia cells. Eur J Cancer Clin Oncol 19: 1067
29. Wiley JS, Taupin J, Jamieson GP, Snook M, Sawyer WH, Finch LR (1985) Cytosine arabinoside transport and metabolism in acute leukemia and T-cell lymphoblastic lymphoma. J Clin Invest 75: 632
30. Wohlhueter RM, Plagemann PGW (1980) The roles of transport and phosphorylation in nutrient uptake in cultured animal cells. Int Rev Cytol 64: 171