

Arabinosyl Cytosine: A Useful Agent in the Treatment of Acute Leukemia in Adults

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ARABINOSYL CYTOSINE (ara-C) is a synthetic pyrimidine nucleoside differing in the sugar moiety from the normal metabolites cytidine and deoxycytidine. (Fig. 1). It is cytotoxic to mammalian cells in culture,¹ inhibits a number of DNA viruses,^{2,3,4} and shows in vivo antitumor activity against leukemia L1210^{5,6} and a variety of transplanted rodent neoplasms.^{7,8}

Talley and Vaitkevicius⁹ reported a series of 13 patients treated with ara-C. These investigators administered the drug intravenously rapidly with doses

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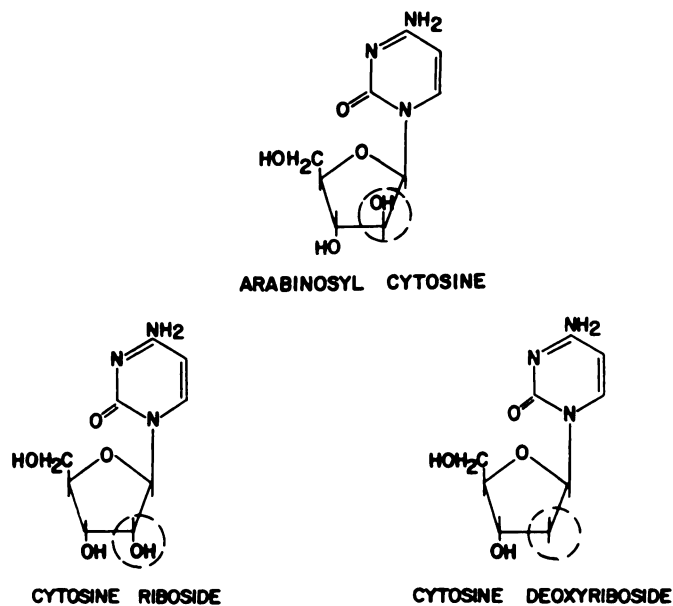


Fig. 1.—Structures of arabinosyl cytosine and the normal metabolites cytidine and deoxycytidine.

ranging from 3 to 10 mg./Kg. daily for 4 to 9 days. They gave a total dose (with daily injections) of not more than 50 mg./Kg. or a single dose of 30–50 mg./Kg. repeated at 7 to 10 day intervals. There was transient regression of adenopathy in three patients with lymphosarcoma. The patients developed leukopenia and thrombocytopenia (which had been expected from pharmacologic study in dogs), marked megaloblastic changes in the marrow and abnormalities of mitosis of hematopoietic cells (which had not been seen in animal studies).

The effectiveness and toxicity of ara-C in leukemic mice varied with the schedule of drug administration. A daily intraperitoneal dose of ara-C produced a greater increase in survival in animals bearing leukemia L1210 (treated either early or late in the course of the disease) than did a single large weekly dose.⁵ It was also demonstrated that ara-C given 4 times daily increased the survival time of animals with advanced leukemia more than any of the other less frequent dosage schedule.⁵ Ara-C was found to be rapidly deaminated in vivo.¹⁰ The pharmacology of continuous intravenous infusion of ara-C in humans was studied in patients with advanced cancer based on the finding that more frequent administration of ara-C yielded better results in mouse leukemia. Frequent administration or continuous administration hopefully would maintain pharmacologically active blood levels at a times (recognizing the inability to detect circulating ara-C at the doses used by available methods). Using a 7 day course, we found that the total dose of ara-C producing hematologic depression is less with continuous infusion than that reported with single daily injections.^{11,12} The hematologic abnor-

malities developing in patients receiving 30 mg./m.²/day for 7 days by continuous infusion were comparable to those reported by Talley after a 7-fold greater total dose divided into four to nine daily injections.

Preliminary work done during the course of the pharmacologic study indicated that ara-C given by continuous infusion had antileukemic activity in adults with acute myelocytic leukemia. The Acute Leukemia Group B (ALB), then initiated a study of the treatment of acute leukemia in adults with ara-C at several doses given by continuous intravenous infusion.¹³ This was followed by a study of daily infusions of varying durations. Both studies will be reported in this paper. Some of these patients have been previously described.¹⁴

METHOD OF STUDY

All adults with acute leukemia in relapse were eligible for inclusion in study regardless of morphologic type, clinical status, previous treatment, elevation of leukocyte count, degree of bleeding, or other considerations. In the first study, ALB 6503, nearly all of the patients were treated at three institutions. In the second study, ALB 6606, 13 of the institutions in the Group contributed cases.

In ALB 6503, patients were randomized between two daily doses, 10 mg./m.²/day and 30 mg./m.²/day. It was intended that all patients be treated with continuous infusion for 24 hours a day. Because of problems in hospitalizing a large population of patients, one institution (with 54 per cent of the cases) gave the drug during a 12 hour period in the clinic rather than for 24 hours. Provision was made for downward modification of daily dose based on the leukocyte level and evidence of definite platelet depression caused by the drug (and/or the production of gastrointestinal tract ulceration), but it was stipulated that such downward modification be monitored by estimates of marrow cellularity rather than be dependent solely on the peripheral counts. Thus, drug was not discontinued unless remission or a hypoplastic marrow resulted. Progressive fall of the peripheral white count to levels below 1000/mm³ was followed by a decrease of the daily dose to 1/2 if marrow was still cellular and leukemic. If further progression of leukopenia and/or production of marrow hypocellularity had not occurred after one week, full dose was resumed. The protocol also specified an increase in dose by 50 per cent at one week intervals if the white count remained at more than one-half the original level and the marrow was not hypocellular. This provision, however, was not regularly followed. The aim throughout was to continue drug administration during the induction phase to the point of maximum tolerable amount, i.e., the production of marrow hypocellularity without the development of fatal sepsis and/or bleeding.

As the first study proceeded, one of the two initial drug doses, 10 mg./m.², was discontinued. All subsequent patients in this study received 30 mg./m.²/day in the induction phase. Once marrow response occurred and marrow hypocellularity cleared, patients entered the maintenance phase. At first they were randomized into two groups, one group receiving no drug and one receiving 30 mg./m.² weekly subcutaneously. When the use of maintenance drug was shown to be effective, the randomization was changed to 30 mg./m.² subcutaneously once weekly vs. twice weekly for maintenance.

In the second study, designated ALB 6606, we attempted to determine whether the optimal period for daily drug administration fell somewhere between 10 minutes (as tested by others) and 12 or 24 hours. Initially patients entering the study were randomized between doses of 30 mg./m.²/day given over a one hour period and the same dose given over a 4 hour period. While we again aimed at marrow hypocellularity as an end point, cut off from further treatment was allowed at a total dose of 1000 mg./m.² if no improvement was noted. When we found that the one hour dose at this level was relatively less active in depressing the bone marrow, the randomization was changed to allow for three groups receiving 50 or 100 mg./m.²/day in one hour, or 30 mg./m.²/day over 4 hours. The aim of marrow hypocellularity was again stressed at this

Table 1.—*Study of Arabinosyl Cytosine in Acute Leukemia of Adults*

	12 or 24 hr. infus. ALB 6503	1 or 4 hr. infus. ALB 6606
Randomized Cases	117	117
Cases Invalidated		
died before drug given		3
transferred out of study		2
gross alteration of dosage regimen		3
previous ara-C response and relapse		1
cause of response not clear	1	3
acute leukemia following polycyth. vera		1
no records received		3
Cases Evaluated in Paper	116	101
acute myelocytic	98	82
acute lymphoblastic	9	14
acute unclassified	9	5

time and allowance was made for the 4-hour dose to be increased to 60 and then 100 mg./m.² if marrow cellularity had not yet decreased and the leukocyte level was stable even if leukopenic. Maintenance treatment in this study consisted of either 30 mg./m.² twice weekly subcutaneously, or 5 consecutive days of ara-C given intravenously (at the dose which produced remission) every 4 weeks.

Throughout both studies, supportive therapy, including platelet transfusions, was used where indicated and feasible. Multiple platelet transfusions were more readily available in the three institutions contributing the bulk of the cases in the first study. Because of this supportive measure, the possibility exists that a higher proportion of patients in the first study were treated more vigorously than many in the second study.

Responses were evaluated by the criteria of Acute Leukemia Group B.* In the results to be discussed, only complete (CR) or partial (PR) remission are considered significant. Marrow and/or peripheral blood remission in the presence of progression or persistence

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*Disease status A requires the following: In the marrow there must be no more than 5 per cent blast cells, and 40 per cent or fewer lymphocytes and blast cells in acute lymphocytic leukemia, and no more than 5 per cent blast cells, promyelocytes, monocytoid cells or other elements which cannot be classified as more mature normal elements in acute myelocytic leukemia. Bone marrows qualifying for such M1 ratings must also contain qualitatively and quantitatively normal erythropoiesis, granulopoiesis, and megakaryopoiesis (except for drug induced changes, such as megaloblastosis). To classify as a complete remission, adult males must also have at least 12 Gm. per cent hemoglobin, (11 Gm. per cent for females), with at least 1500 mature neutrophilic granulocytes/cu. mm. in the peripheral blood. A patient must have a rating of 1 in all categories (including physical signs and symptoms as well as marrow and blood) for a disease status A ("no evident disease"), and there must be improvement to disease status A for a response to be considered a complete remission.

Disease status B implies a rating of 2 in one or more of the 4 categories, but no rating of 3 in any category. For such a rating, the bone marrow in a patient with acute myelocytic leukemia must contain from 5.1 to 25 per cent blast cells. A rating of 2 for the hemogram implies a hemoglobin of at least 7 Gm. (with maintenance of this not attributable to transfusion), at least 500 mature neutrophilic granulocytes/cu. mm., 25,000 to 100,000 platelets/cu. mm., and no more than 5 per cent blasts in the peripheral blood.

Table 2.—Response of Adults with Acute Leukemia to 12 or 24 Hour Daily Infusions of Arabinosyl Cytosine

Dx	Infus. time hrs./day	Daily dose mg./m. ²	Total # Rxed	# Evaluable	CR	PR
AML	12	10	12	12	2	—
		30	41	41	10*	2
	24	10	9	9	2	—
		30	36	36	2	5
ALL	12	10	1	1	—	1
		30	4	3	1*	—
	24	10	1	1	—	—
		30	5	5	—	1
AUL	12	10	1	1	1	—
		30	5	5	1	—
	24	10	1	1	1	—
		30	2	2	—	—

* = 1 patient with complete remission except for hemoglobin level.

of disease elsewhere, i.e., node involvement, hepatosplenomegaly, etc. is not included among remissions.

In some instances where severe bleeding developed in the course of treatments with ara-C, patients received adrenal corticosteroid therapy. Special notation will be made when response of the leukemia occurred in patients who were also given steroid. In most instances, when a steroid was used, remission did not occur and therefore it was not necessary to disqualify such cases from this study. Development of meningeal leukemia in the absence of any other sign of relapse did not remove the patient from the study, nor did the use of intrathecal methotrexate with systemic citrovorum factor in such patients.

Table 1 gives an overall summary of the number of patients with acute leukemia entered in the two studies described above. The group designated as acute myelocytic leukemia (AML) includes all patients diagnosed as myeloblastic, acute myelocytic, myelomonocytic, monocytic, or erythro-leukemia. In addition to the 217 evaluable adults with acute leukemia, a number of adults in the "acute" phase of chronic myelocytic leukemia were studied, with the dose chosen nonrandomly during the course of the two protocols described. Following this, a small group of patients with "acute" phase of chronic myelocytic leukemia were entered into a study in which treatment consisted of 30 mg./ml/day given during 4 or 12 hours.

RESULTS

ALB 6503

The results of the first study are summarized in Table 2. Of the adults who received 30 mg./m.²/day, 25 per cent of 77 with AML and 20 per cent of 15 with acute unclassified leukemia (AUL) or acute lymphocytic leukemia (ALL) responded with complete or partial remission. These partial remissions usually fell only slightly short of being classifiable as complete. All types of leukemia responded. A similar response rate (19 per cent of 21 with AML and all of 3 with AUL or ALL) was seen in the smaller group of patients treated with 10 mg./m.²/day, with the majority of responses being complete. At the higher dose level, relatively more of the responses were complete in the group

Table 3.—Toxic Effects of 12 or 24 Hour Daily Infusions of Arabinosyl Cytosine in Adults with Acute Leukemia

	30 mg./m. ² /day	10 mg./m. ² /day
	%	%
Fall to WBC 1.0 – 1.9	9	8
<1.0	45	21
Definite platelet fall	42	29
Marrow hypocellularity	39	29
Gastrointestinal tract:		
ulcers _c or _s other effects	3	0
N & V and/or diarrhea, no ulcers	1	4
Phlebitis*	8	8
Total no. patients	92	24

*Numbers represent a minimum figure. Information on this not always recorded.

treated for 12 hours a day. Two of the patients in the 24 hour group who were categorized as partial remissions may actually have been complete remissions, however, (see Table 4, footnotes) so that it is difficult to say whether this is an important difference.

There were 22 per cent complete remissions plus partial remissions in the 73 patients with AML who were previously untreated or whose previous treatment lasted less than two weeks and 28 per cent in the 25 who were treated for two weeks or more with other agents prior to receiving ara-C. Thus there was no appreciable difference in response related to previous treatment.

The total amounts of ara-C. administered during the induction phase varied widely. Few responses were produced with less than 200 or more than 1000 mg./m.² total drug dose. In 12 instances retrospective review of the data suggests that drug trial was inadequate, i.e., more drug could have been tolerated.

The incidence and degree of drug toxicity was greater at 30 than at 10 mg./m.² with the predominant effects being those related to marrow depression (Table 3). Platelet depression was prominent and platelet transfusions were frequently used. Since we stopped treatment at the first evidence of marrow depression, there may have been some "overshoot" with the higher dose due to drug already given before leukopenia occurred. The gastrointestinal effects were less frequent at both doses than that reported by others using once daily drug administration.

In 49 of the 116 randomized cases, data concerning liver function tests are adequate for analysis. Abnormalities were present in 7 before ara-C administration. They disappeared in 4 of these and remained unchanged in the other 3. Of the 42 with normal liver function tests before ara-C, 25 remained normal, 7 had significant bilirubin elevations coincident with either sepsis (5), a hemolytic reaction to platelet transfusion (1), or widespread hemorrhage (1), 5 had bilirubin elevation to < 3 mg. per cent with return to normal on continued drug administration, 4 had minor variations in SGOT

and/or alkaline phosphatase and/or bilirubin with return to normal during treatment, and 1 developed marked abnormalities of all three tests 2 months after ara-C. In this last patient, the picture was that of serum hepatitis, and he has not had a recurrence during subsequent courses of cytosine arabinoside during the ensuing 18 months. Two nonrandomized cases (with diagnoses of acute leukemic phase of lymphosarcoma and acute phase of chronic myelocytic leukemia) also developed a similar picture. Only one of those 2 was subsequently retreated with ara-C and there was no recurrence of jaundice. Thus there was no definite evidence of hepatotoxicity.

The first improvement in marrow rating was noted 1 to 9 weeks after the start of ara-C, with a median of 4 weeks in both dose groups. There may have been a slightly earlier evidence of response in the 12 hour infusion group than in the 24 hour infusion group ($3\frac{1}{2}$ vs. $4\frac{1}{2}$ wks). However, a median total of 480 mg./m.² of drug with a range of 120 to 945 mg. was necessary at both doses. Thus, 3 times as many days of i.v. infusion were necessary at the lower daily dose to produce an equal drug effect. This also indicates that the first evidence of marrow improvement was seen during the course of treatment at the lower dose but appeared *after* the drug had already been discontinued (usually because of marrow depression) in those who received the higher dose.

Table 4 gives details concerning the responsive patients. Where prednisone was used in these patients (predominantly during bleeding episodes) the amount or timing of the doses were such that the responses did not appear to be related to the use of steroid.

Responses occurred at all age levels treated. When the age distribution of the responders is compared with the age distribution of all the patients with acute myelocytic leukemia treated with ara-C, no relationship of age to response rate can be seen. There was only one response in a patient with an initial white count of over 100,000/cu. mm. but skewing of the distribution of responders towards the leukopenic patients did not occur. Analysis of the pretreatment platelet level indicates an equal response rate in the markedly and moderately thrombocytopenic patients but a higher response rate in those whose platelets were 100,000/mm.³ or greater at the time ara-C was started.

Four patients included in the 98 designated and evaluated as AML in ALB 6503 were diagnosed as cases of erythroleukemia by the contributing institutions. One of these 4 sustained a partial remission (complete except for hemoglobin which never rose above 11 Gm. per cent). An additional 8 patients in this group had 31–61 per cent nucleated red blood cells in their marrows at the start of ara-C treatment as well as abnormal numbers of myeloblasts. One complete and one partial remission occurred. Other marrow improvement occurred only at the expense of the erythroid elements and with no peripheral blood improvement. The response rate of this group of patients (25 per cent of 12) therefore did not differ from that of AML as a whole.

Once remission was induced, patients were allocated at random to receive either no drug or 30 mg./m.² ara-C subcutaneously once a week. A marked increase in duration of remission was produced by drug administration. All

Table 4.—Summary of Pertinent Data in Adults with Acute Leukemia Responding to 12 or 24 Hour Daily Infusions of Arabinosyl Cytosine

Age	Init. WBC	Status pre Ara-C					Induction phase				Response to Drug					Maintenance Phase				Survival days from start Ara-C		
		>2 wks prev. Rx	pre Rx				daily	infus. dose mg./m. ²	total dose hrs.	M2	M1	marrow hypocell.	best*			day of relapse M2	M3	duration marrow response days	Response to 2nd course			
			M	H	P	S							M	H	P							
AML																						
23	112.	—	3	3	2	3	10	12	630	prednisone 50	17	59	x	1	1	1	1	223	251	206	332	335
36	4.4	—	3	3	2	1	10	12	880	—	20	85	x	1	1	1	1	O.W.	117	97	230	233
54	4.6	x	2	3	1	2	10	24	255	—	(45)†	75	x	1	1	1	1	187	142	142	CR	761+
18	34.	—	3	3	2	2	10	24	470	prednisone 20	30	57	x	1	1	1	1	O.W.	158	128	CR	485
36	10.	—	3	3	3	3	30	12	120	—	19	25	x	1	1	1	1	54	88	35	—	126
66	2.6	—	3	3	2	3	30	12	450	—	25	42	x	1	1	1	1	O.W.	577+	577+	602+	610+
36	2.8	—	3	3	1	2	30	12	480	—	13	48	x	1	1	1	1	B.I.W.	330	317	467+	476+
71	3.4	—	3	3	2	2	30	12	945	—	25	48	x	1	1	1	1	O.W.	236	211	270	288
61	20.	—	3	3	2	1	30	12	630	—	14	32	x	1	1	1	1	O.W.	255	223	511	514
27	0.8	—	3	3	2	2	30	12	660	prednisone 40	40	76	x	1	1	1	1	507	467	567+	570+	570+
72	1.2	—	3	3	2	3	30	12	390	—	38	x	1	1	1	1	1	137	99	177	188	188
57	10.4	—	3	3	2	2	30	12	780	—	7	38	x	1	1	1	1	O.W.	135	128	135	152
55	0.6	—	3	3	3	3	30	12	360	—	24	x	1	1	1	1	1	O.W.	202	178	290	290
24	23.	x	3	3	2	2	30	12	360	I.T. MTX	12	7	?	1	2†	1	1	44	32	32	PR	144
50	13.	—	2	3	2	2	30	12	420	prednisone 20	49	7	x	1	2	1	1	O.W.	35	28	315+	358+
76	56.	—	3	3	2	3	30	12	540	—	22	64	?	2	2	1	2	B.I.W.	?	739	128	130
30	2.5	x	3	3	1	1	30	24	277	—	22	64	x	1	1	1	1	O.W.	244	222	533+	597+
72	1.9	x	2	3	2	3	30	24	480	—	46	x	1	1	1	1	1	74	95	28	—	174
25	60.	—	3	3	3	3	30	24	900	—	50	59	x	1	1	(2)§	165	115	555+	560+	560+	
71	1.1	x	2	3	2	2	30	24	330	—	(31)†	43	x	1	2	2	—	77	46	125	305	305
19	70.	x	3	3	2	2	30	24	697	prednisone 20	64	52	x	2	2	1	1	B.I.W.	129	65	251	2391
21.	21.	x	3	3	2	1	30	24	652	—	31	52	x	1	1	(2)¶	123	137	92	197	408	
54	93.	—	3	3	2	3	30	24	772	—	39	39	x	2	1	1	1	B.I.W.	103	64	118	121
ALL and AUL																						
54	2.2	—	3	2	2	1	10	12	760	I.T. MTX	23	99	x	1	1	1	1	O.W.	268	245	287	305
68	40.	—	3	3	—	—	10	12	470	—	56	7	?	2	2	—	—	94	38	161	169	169
62	1.2	—	3	3	2	3	10	24	305	—	29	±	1	1	1	1	1	—	293	264	CR	727+
76	1.6	—	3	3	2	2	30	12	480	—	33	x	1	1	1	1	1	O.W.	379	407	415+	433+
23	2.2	x	3	2	2	1	30	12	390	—	36	7	1	2	1	1	1	—	72	94	129	546
18	8.6	—	3	3	2	3	30	24	190	—	24	x	2	2	1	1	1	31	7	impr.	502	505

*See footnote in text for definition of remission ratings in marrow (M), hematologic findings (H), physical signs (P), and symptoms (S).

†Significantly improved M2.

‡H1 except hemoglobin.

§Equivalent retroperitoneal adenopathy.

¶Neurological deficit presumably due to prior Vincristine.

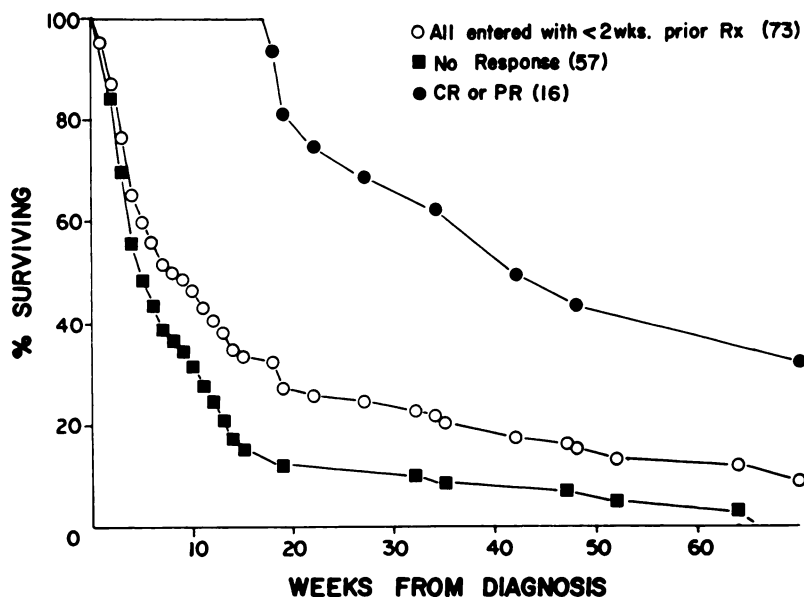


Fig. 2.—Survival from diagnosis of 73 previously untreated adults with acute myelocytic leukemia given 12 or 24 hour daily infusions of arabinosyl cytosine (ALB #6503). Those who had either a complete remission (CR) or a partial remission (PR) had a longer survival than did those with no response.

of the unmaintained patients have relapsed, with a median remission duration of 5 weeks. One of the 13 patients treated once weekly is still in remission at 577 days; the median for this group is 30 weeks. When the advantage of remission maintenance became obvious, the randomization was changed to include a group receiving subcutaneous ara-C 30 mg./m.² twice weekly. This gave poor results (median duration of remission of 9 weeks), but only five patients in this study were entered on this dose.

In assessing the results of treatment in patients with leukemia, enumeration of the response rate is not sufficient to indicate the extent of drug effect. The survival of the group must also be considered. As already noted, the 28 per cent response rate seen in those patients with acute myelocytic leukemia who were previously treated does not differ from the 22 per cent rate noted in patients who had received little or no treatment prior to ara-C. Most of the former group had had at least one remission on other therapy prior to receiving ara-C and thus represented a selected group. It seemed more appropriate, therefore, to analyze separately the 73 patients who had received little or no treatment before ara-C. Nine of the 16 responders in this group are still alive. The survival of the patients with remissions was markedly longer than that of the rest of the group (Fig. 2). However, survival of the group as a whole is disturbingly short. We therefore attempted to compare these data with others obtained by the Leukemia Group B in adults with acute myelocytic leukemia. In a group of 855 such patients (which included all those seen by the cooperating institutions where previously treated or not), an age related

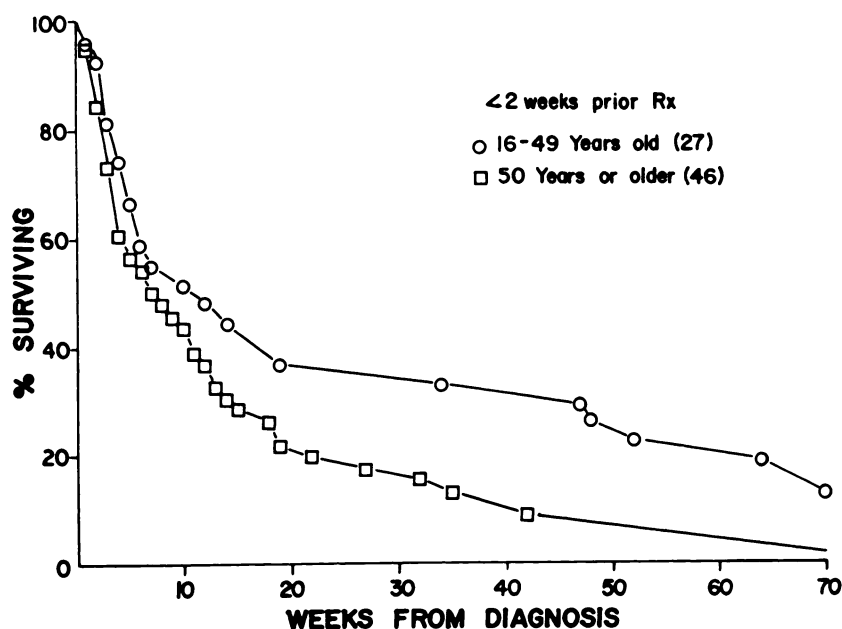


Fig. 3.—Survival from diagnosis of 73 previously untreated adults with acute myelocytic leukemia given 12 or 24 hour daily infusions of arabinosyl cytosine (ALB #6503): comparison of results in two age groups, 16–49 and 50 years or older.

difference was demonstrated, with patients under 50 having a longer median survival time. Similar age related differences occurred in the 73 previously untreated adults with acute myelocytic leukemia who received ara-C in the first study (Fig. 3). Such differences were noted both in the responsive and nonresponsive patients. When compared with the earlier accumulated data on survival time, the younger previously untreated ara-C patients did poorly, although the entire younger ara-C group was comparable. Neither group, however, is completely equivalent in content to the ALB control experience.

The early death rate in the older previously untreated patients given ara-C does not differ from that previously obtained.

We attempted, therefore, to determine the cause of the early deaths and studied the relationship between the production of hematologic toxicity and the time of death in the nonresponsive patients. Among the 87 nonresponsive patients, 32 were on study for less than 3 weeks, with 29 of these patients dying in less than 3 weeks. Three-quarters of these 29 patients showed no evidence of drug toxicity, whereas 2 deaths were possibly, and 1 death was probably related to drug effects. In those who continued on study longer without response, however, and who were subjected to continued drug administration, more marrow depression was seen. Thus, among 36 patients on study for 3 to 6 weeks, 19 died during the time on study with 9 of these deaths apparently related to drug toxicity. Among 18 patients on study for 6 to 12 weeks, 9 died during this 6 to 12 week interval with two deaths probably related to

Table 5.—Response of Adults with Acute Leukemia to 1 or 4 Hour Daily Infusions of Arabinosyl Cytosine

Dx	Infus. time hrs./day	Daily Dose mg./m ²	Total # Rxed	# Evaluable	CR	PR
AUM	1	30	18	16	3*	1
		50	20	20	6*	—
		100	24	20	5	1
	4	30	31	26	3	1
ALL	1	30	3	3	1	—
		50	2	1	—	—
		100	1	1	—	—
	4	30	9	9	1†	1
AUL	1	30	2	2	—	—
	4	30	4	3	—	—

* = 1 pts. with CR except Hgb level.

† = response related to prednisone administration.

drug toxicity. One patient was on study more than 12 weeks before being transferred to other therapy. The occurrence of drug related deaths during the third to twelfth week of study does not account, however, for the steep slope of the survival curve during the first month of treatment.

Twenty-five per cent of the responders, 20 per cent of the entire group, and 27 per cent of the 29 who died in less than 3 weeks received the lower daily dose (10 mg./m.²). It is worth noting, however, that only 2 of the 17 nonresponders on the lower dose ever developed hematologic depression and neither of these died as a result of such depression. Thus, the early deaths were due to disease at both daily drug levels, and the later deaths were disease related in those treated with the lower dose but were more apt to be drug related in those treated with 30 mg./m.²/day.

Fifty-one of the 87 nonresponsive patients died while on study: 15 of bleeding (9 CNS, 2 GI, 4 other), 14 of sepsis, 4 of pulmonary infection, 2 of infection and bleeding, 3 of renal dysfunction, and 4 of miscellaneous causes. In 9 the cause of death is not known. There was a preponderance of deaths resulting from infection in the cases where death seemed to be related to drug toxicity. The proportion of deaths due to infection was smaller for those in whom death was not related to drug toxicity.

ALB 6606

The second study was planned to test the effectiveness of more rapidly administered doses of ara-C. Initially, we used the same total dose as that used in ALB 6503, 30 mg./m.²/day, but we gave the drug for either 4 hours or 1 hour. With the 1 hour infusion the appearance of marrow depression was delayed. Since we knew that a greater total dose is tolerated in nonleukemic patients when the drug is given once daily than when it is given by 24 hour infusion, we felt that an increase in the 1 hour dosage was indicated. Therefore, we set up a new randomization as described under Method of

Table 6.—Toxic Effects of 1 or 4 Hour Daily Infusions of Arabinosyl Cytosine in Adults with Acute Leukemia

Infusion Time Hrs./day	1			4
Daily Dose—mg./m. ²	30	50	100	30
	%	%	%	%
Fall to WBC 1.0—1.9	24	5	14	37
<1.0	38	19	24	16
Definite Platelet Fall	86	62	57	61
Marrow Hypocellularity	48	33	48	18
Gastrointestinal Tract				
Ulcers c or s other effects	10	10	10	8
N & V and/or diarrhea				
s ulcers	14	14	19	13
Total Number of Patients	21	21	21	38

Study. The results of this study are summarized in Table 5. The response rate does not differ significantly from that obtained with the longer infusions, although the total dose given during the induction period was somewhat higher in the 4 hour infusion (median 765 mg./m.²) and definitely higher in the 1 hour infusion (median 950 mg./m.² with 50 mg./m.² daily dose and 2300 mg./m.² daily dose) than in the previous study.

The pattern of response was similar to that seen in the first study with remissions occurring in patients from the age of 18 through 76 and in patients whose pretreatment leukocyte level ranged from 1700 to 184,000/cu. mm.

There were three responses (1 complete remission, 1 remission complete except for hemoglobin, and 1 partial remission) among the 5 cases of AML labelled as erythroleukemia by the contributing institutions. An additional 10 patients treated in ALB 6606 had 33–55 per cent nucleated red blood cells in their marrow as well as abnormal numbers of myeloblasts at the start of ara-C treatment. There were one complete remission and two remissions complete except for hemoglobin level among these 10. Thus, a response rate of 40 per cent was seen in this group of 15 patients.

The incidence and types of toxicity are shown in Table 6. The gastrointestinal effects occurred more frequently than did those after the same daily dose spread out over a longer period of time, while the marrow depression was not any more marked.

Adequate data on hepatic function were available in 50 of the randomized cases. One among 7 with initial abnormalities showed an increase in SGOT while the other 6 had clearing on treatment. Of the 43 initially normal, 37 remained so, 4 developed significant abnormalities with sepsis and 2 had SGOT and/or alkaline phosphatase changes which reverted to normal while still on drug.

The maintenance course was randomized in 23 patients, 13 receiving twice weekly subcutaneous ara-C and 10 receiving intensive intravenous treatment,

five days per month. The duration of remissions to date in the twice weekly maintenance group ranged from 2½ to 35+ weeks (median 11½ wks) with 2 patients still in remission. The median of the combined twice weekly maintenance data of ALB 6503 and ALB 6606 was also 11½ weeks.

In the group treated 5 days per month, remissions lasted for 4 to 44 weeks (median 14 weeks) with 2 of these patients still in remission. One of the patients relapsed during the first five day maintenance course.

Data on survival in this second study are not presented in detail because of the preponderance of previously treated patients among those with AML. The pattern of longer survival among those who sustained complete or partial remissions as described for ALB 6503 was again noted in ALB 6606.

Children—Acute Leukemia

Although the protocols included only adults in the randomization schema, 31 children received ara-C, with results similar to those seen in adults with AML. Dosage regimens followed included all of those previously outlined in 27 instances. A higher dose (100 mg./m.²/day by 24 hour infusion) was used in 4 children. There are too few in any one treatment group to warrant discussing these separately. There were 2 complete remissions, 1 remission complete except for hemoglobin level, and 4 partial remissions among 17 children with AML. Five of these responses occurred in the 14 of these 17 who had had prior treatment. Two of the 3 previously untreated children responded. One of the 3 children with AML treated at the higher dose level responded. The responses lasted from 14 to 378+ days (median 56 days). Two of the 14 children with ALL had partial remissions lasting only two weeks.

Acute Phase of Chronic Myelocytic Leukemia

Only one complete and one partial remission resulted from treatment of this disease with ara-C by a variety of regimens in 19 patients, despite the production of leukopenia of <2,000 WBC/cu. mm. in 12 and marrow hypocellularity in 7. The partial remission lasted 43 days but the planned twice weekly maintenance was given irregularly in this patient because of recurrent thrombocytopenia. The other responder had 70 days of complete remission and 146 days of partial remission (blasts + promyelocytes in marrow ranged from 6–15 per cent although blood counts were normal). The latter patient however, did not have a Ph¹ chromosome and had had only a brief atypical period of hematologic abnormality prior to the appearance of a blastic phase. This may be a “subacute” form of AML rather than the “acute” phase of CML. Following relapse he has not had a clear cut response to repeated courses of ara-C although there was a subsequent rise in hemoglobin to normal.

Acute Leukemic Phase of Lymphosarcoma or Reticulum Cell Sarcoma

There was definite to marked decrease of hepatosplenomegaly and lymphadenopathy at the time that marrow hypocellularity occurred following use of ara-C in three such patients, but this was without clinical benefit. All three died; two of bacterial sepsis and one of generalized herpes zoster. A fourth patient who also developed marrow hypocellularity had no change in

massive hepatosplenomegaly but had improvement in marrow status from M3 to M2 for 40 days, accompanied by more prolonged improvement of hemoglobin and platelet levels and peripheral differential (hematologic status H3 improved to H2).

DISCUSSION

Arabinosyl cytosine, a compound of known activity in mouse leukemia,^{5,6} has now been tested in a variety of dosage regimens in acute leukemia, and has been found to be active in the treatment of adults with acute myelocytic and acute lymphocytic leukemia. As would be expected in the treatment of acute leukemia in adults, a preponderance of the patients had a diagnosis of acute myelocytic leukemia. This designation included all patients diagnosed as having myeloblastic, acute myelocytic, myelomonocytic, monocytic, or erythroleukemia. Significant responses were noted in all such types of leukemia and survival time was prolonged in those patients who had complete or partial remissions.

Responses occurred at all age levels among the adults. In a smaller group of children treated in the course of the study, the response rate in AML was at least as good as for the adults. Remissions were seen in patients regardless of the pretreatment leukocyte level. Presence of a low platelet count before treatment prejudiced unfavorably the chance of response to treatment.

The dosage regimens used included infusions lasting 1, 4, 12 or 24 hours per day, with the drug continued to the point of marrow depression where possible. Responses were noted at all the different infusion durations with an overall rate of 24 per cent complete and partial remissions. Analysis does not reveal a significant difference in response from one group to another, but the number of complete remissions seen after daily 1 hour infusions of 50 or 100 mg./m.² or 12 hour infusions of 30 mg./m.² (25 per cent) suggest that one of these three regimens might be superior to the others tried. The convenience of a one hour infusion is obvious despite the higher incidence of gastrointestinal effects.

Despite the absence of change in therapeutic index, the amount of drug tolerated with different infusion durations varied inversely with the duration of infusion. This is consonant with our previous finding that the total dose of ara-C which produced hematologic depression in nonleukemic subjects was less than that reported with single daily injections.^{9,12} The data indicate that the amount that is necessary for a response in adults with AML is close to the amount that is necessary to produce marrow depression as monitored by the cellularity noted on repeated marrow aspirations. Depression of leukocyte level alone is not sufficient. Platelet depression occurred frequently during the course of treatment and could be limiting in the use of ara-C when platelet transfusions are not available. The gastrointestinal side effects, however, were rarely limiting.

The complete remission rate observed with ara-C in AML in adults is superior to that which has been reported for 6-mercaptopurine given to comparable patients either by daily oral administration,^{15,16,17,18} or by parent-

eral administration once or twice weekly.¹⁹ The combined complete and partial remission rate, however, does not differ greatly from results previously obtained with 6-mercaptopurine. The results with ara-C approach but do not equal those being obtained by Henderson²⁰ in a current ALB study of the effects of a combination of prednisone, vincristine, 6-mercaptopurine, and methotrexate in adults with AML. Cross-resistance between ara-C and these other forms of treatment has not been noted clinically.

Comparison of the ara-C results reported here with those obtained by others²¹ who gave the drug as a single rapid daily injection in adults with AML suggests that the 1 hour infusion of 50 or 100 mg./m.²/day gave a greater proportion of complete remissions, although the overall response rate does not differ. Such a course of therapy with daily 1 hour infusions would take approximately three to six weeks (depending on the daily dose used) to reach the point of necessary but tolerable marrow depression although the dose range may be wide. Appropriate maintenance therapy appears to consist of weekly subcutaneous injections of 30 mg./m.² of ara-C. The availability of platelet transfusions is important for adequate use of ara-C.

SUMMARY

Arabinosyl cytosine (ara-C), a synthetic pyrimidine nucleoside related to the normal metabolites cytidine and deoxycytidine, has been found capable of producing marrow remission at tolerable doses in acute myelocytic and acute lymphocytic leukemia in adults. There were 16 per cent remissions complete in all aspects, 3 per cent complete except for hemoglobin level, and 6 per cent partial remissions among 180 adults with acute myelocytic leukemia treated with any one of 8 variants of infusion duration or daily dose of ara-C. Twenty-four per cent of 37 adults with acute lymphocytic or unclassified leukemia had complete or partial remissions. The comparison of 1, 4, 12 and 24 hours infusion of ara-C (to total dose tolerated) does not show significant superiority for any one group. The *complete* remission rate with 1 or 12 hour infusions, however, is 25 per cent (superior to that obtained with 6-mercaptopurine) and the recommended schedule of treatment for ara-C based on these data is, therefore, daily infusions of 100 or 50 mg./m.² in one hour for approximately 3 to 6 weeks followed by maintenance therapy of once weekly subcutaneous injection of 30 mg./m.² of ara-C. Platelet transfusions should be available when ara-C is used.

SUMMARIO IN INTERLINGUA

Cytosina arabinosylic (C-ara), un synthetic nucleosida de pyrimidina relationate al normal metabolitos cytidina e desoxycytidina, se ha monstrate capace de producer remission medullari a tolerabile nivellos de dosage in acute leucemia myelocytic e lymphocytic in adultos. Inter 180 adultos con acute leucemia myelocytic tractate con octo variantes de programma therapeutic (i.e., variationes in le duration del infusion o del dosage diurne de C-ara), 16 pro cento respondeva con complete remissiones in omne le aspectos del morbo, durante que 3 pro cento additional respondeva con complete remissiones excepte in le nivellos de hemoglobina. In plus, 6 pro cento monstrava como responsa un remission partial. Inter 37 adultos con acute leucemia lymphocytic o nonclassificate, 24 pro cento respondeva con remissiones complete o partial. Le comparison inter le resultatos obtenite

per le infusion del total tolerate dose diurne in 1, 4, 12, e 24 horas non revela ulle superioritate significative de un del gruppis super le alteres. Tamen, le incidentia de remission complete pro infusiones de 1 o 12 horas esseva 25 pro cento (lo que es superior al resultados obtenite con 6-mercaptopurina), e le recommendate programma de tractamento con C-ara base de iste datos es, per consequente, le application de infusiones diurne de 100 o 50 mg per m² in un hora durante approximativemente 3 a 6 septimanas, sequite de un therapia de mantenentia de injectiones subcutanee de 30 mg per m² de C-ara a intervallos de un septimana. Quando C-ara es usate, il es necesse provider pro le possibilitate, a omne tempore, de effectuar transfusiones de plachettas.

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