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

By ROSE RUTH ELLISON, JAMES F. HOLLAND, MARISE WEIL, CLAUDE JACQUILLAT, MICHEL BOIRON, JEAN BERNARD, ARTHUR SAWITSKY, FRED ROSNER, BERNARD GUSSOFF, RICHARD T. SILVER, ARTHUR KARANAS, JANET CUTTNER, CHARLES L. SPURR, DONALD M. HAYES, JOHANNES BLOM, LOUIS A. LEONE, FARID HAURANI, ROBERT KYLE, J. L. HUTCHISON, R. JACKSON FORCIER AND JOHN H. MOON

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 Vaitkevicius[9] reported a series of 13 patients treated with ara-C. These investigators administered the drug intravenously rapidly with doses

From the Acute Leukemia Cooperative Group B

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ROSE RUTH ELLISON: *Department of Medicine A, Roswell Park Memorial Institute, Buffalo, New York.* JAMES F. HOLLAND (CA 02599): *Roswell Park Memorial Institute, Buffalo, N. Y.* MARISE WEIL: *Institut de Recherches Sur Les Leucémies, Hôpital Saint-Louis, Paris X^e, France.* CLAUDE JACQUILLAT: *Institut de Recherches Sur Les Leucémies, Hôpital, Saint-Louis, Paris X^e, France.* MICHEL BOIRON: *Institut de Recherches Sur Les Leucémies, Hôpital Saint-Louis, Paris X^e, France.* JEAN BERNARD: *Institut de Recherches Sur Les Leucémies, Hôpital Saint-Louis, Paris X^e, France.* ARTHUR SAWITSKY (CA 05923): *S.U.N.Y., Long Island Jewish Hospital, New Hyde Park, N. Y.* FRED ROSNER (CA 05923): *S.U.N.Y., Maimonides Hospital of Brooklyn, N. Y.* BERNARD GUSSOFF (CA 05923): *S.U.N.Y., Jewish Hospital of Brooklyn, Brooklyn, N. Y.* RICHARD T. SILVER (CA 07968): *New York Hospital, Cornell Medical Center, New York.* ARTHUR KARANAS (CA 07968): *New York Hospital, Cornell Medical Center, New York.* JANET CUTTNER (CA 04457): *Mt. Sinai Hospital, New York, N. Y.* CHARLES L. SPURR (CA 03927): *Bowman Gray School of Medicine, Winston-Salem, N. C.* DONALD M. HAYES (CA 03927): *Bowman Gray School of Medicine, Winston-Salem, N. C.* JOHANNES BLOM: *Walter Reed Army Medical Center, Cancer Chemotherapy Clinic, Washington, D. C.* LOUIS A. LEONE (CA 08025): *Rhode Island Hospital, Providence, R. I.* FARID HAURANI (CA 05462): *Jefferson Medical College Hospital, Philadelphia, Pa.,* ROBERT KYLE (CA 04646): *Mayo Clinic, Rochester, Minn.* J. L. HUTCHINSON: *Montreal General Hospital, Montreal, P. Q., Canada.* R. JACKSON FORCIER (CA 04326): *Dartmouth Medical School Affiliated Hospital, Hitchcock Hospital, Hanover, N. H.* JOHN H. MOON (CA 03735): *Medical College of Virginia, Richmond, Va.*

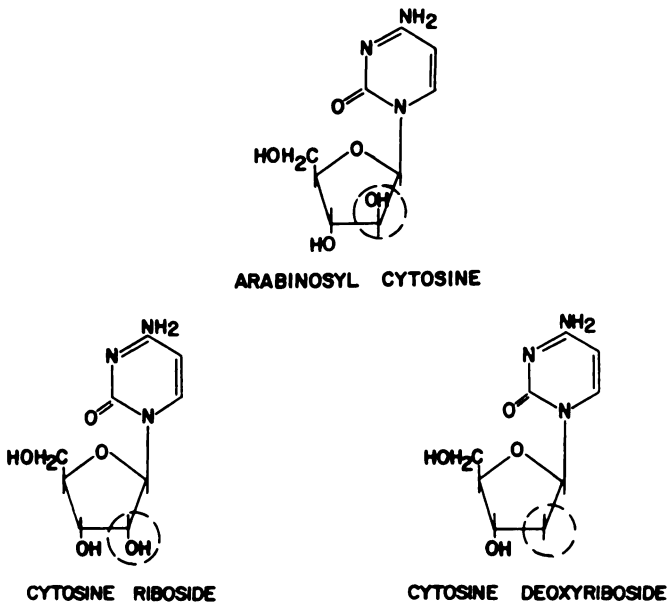

Fig. 1.—Structures of arabinosyl cytosine and the normal metabolites cytidine and deoxycytidine.

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/mm^3 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

*Roswell Park Memorial Institute, Buffalo, New York; Institut de Recherches sur les Leucémies, Paris, France; New York Hospital, Cornell Medical Center, New York, New York.

*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					
		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

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