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Treatment of Early Acute Nonlymphatic Leukemia with Low Dose Cytosine Arabinoside

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Successful induction of remissions in adults with acute nonlymphatic leukemia (ANLL) requires the use of high dose aggressive chemotherapy which is not well tolerated by older adults and few remissions are obtained in patients with ANLL secondary to refractory anemia and other disorders (Moloney and Rosenthal, to be published) For years investigators have attempted to discover methods of producing remissions by inducing leukemic cells to differentiate and recently Sachs (1978) has pointed out that a number of agents were capable of inducing maturation in leukemic mouse myeloblasts. Among the chemical compounds investigated was cytosine arabinoside (Ara-C) an antimetabolite extensively used in high dosage for treatment of ANLL. Based on these experimental findings Baccarani and Tura (1979) treated a patient with refractory anemia and excess myeloblasts in the marrow with a short course of low dose Ara-C and obtained an excellent clinical and hematological improvement with partial bone marrow remission. Encouraged by this report we have treated two patients with early ANLL and seven patients with RDA-ANLL with low dose Ara-C. Observations on these cases and preliminary findings on the effect of low dose Ara-C on leukemic cells cultured in diffusion chambers are presented in this paper.

A. Methods and Materials

Patients were followed and laboratory studies carried out in the Hematology Division of Peter Bent Brigham Hospital. Bone marrow biopsies and aspirates were carried out initially and repeated during the course of the disease. Blood and marrow smears were stained with Wright Giemsa and histochemical methods included those for leucocyte alkaline phosphatase and peroxidase activity; iron stains were carried out routinely on all marrow specimens. Bone marrow cells were cultured in diffusion chambers (DC) implanted in the abdominal cavities of previously irradiated rats. Details of this method have previously been published (Greenberger et al. 1977, 1978). For studies on the effect of low dose Ara-C, host animals were treated by subcutaneous injections daily for 21 days with 0.1 mg Ara-C per kilogram.

B. Clinical Results

Two patients with early de novo ANLL were treated with low dose Ara-C and achieved complete remission.

Case 1 (E.E.): This 78-year-old male had a 6 month history of myalgia and developed progressively severe fever, night sweats, and pain in the back, and chest. There was no hepatosplenomegaly and blood studies were within normal limits except for a rapid E.S.R. As part of a diagnostic work-up a bone marrow biopsy and aspirate were carried out and revealed a hypercellular but variable cell population; some areas were relatively normal but elsewhere sheets of myeloblasts, some containing Auer rods, were present. Treatment with Ara-C 0.8 mg per kilogram (50 mg) s.c. was carried out for 20 days. After one week the patient improved, fever, night sweats and pain ceased and after an initial moderate fall the platelets, WBC, and hematocrit rose to normal levels (Fig. 1). He has been maintained for over 6 months in hematological remission with monthly 5 day courses of Ara-C 0.4 mg daily s.c. Following remission bone marrow aspirations have revealed M1 marrows.

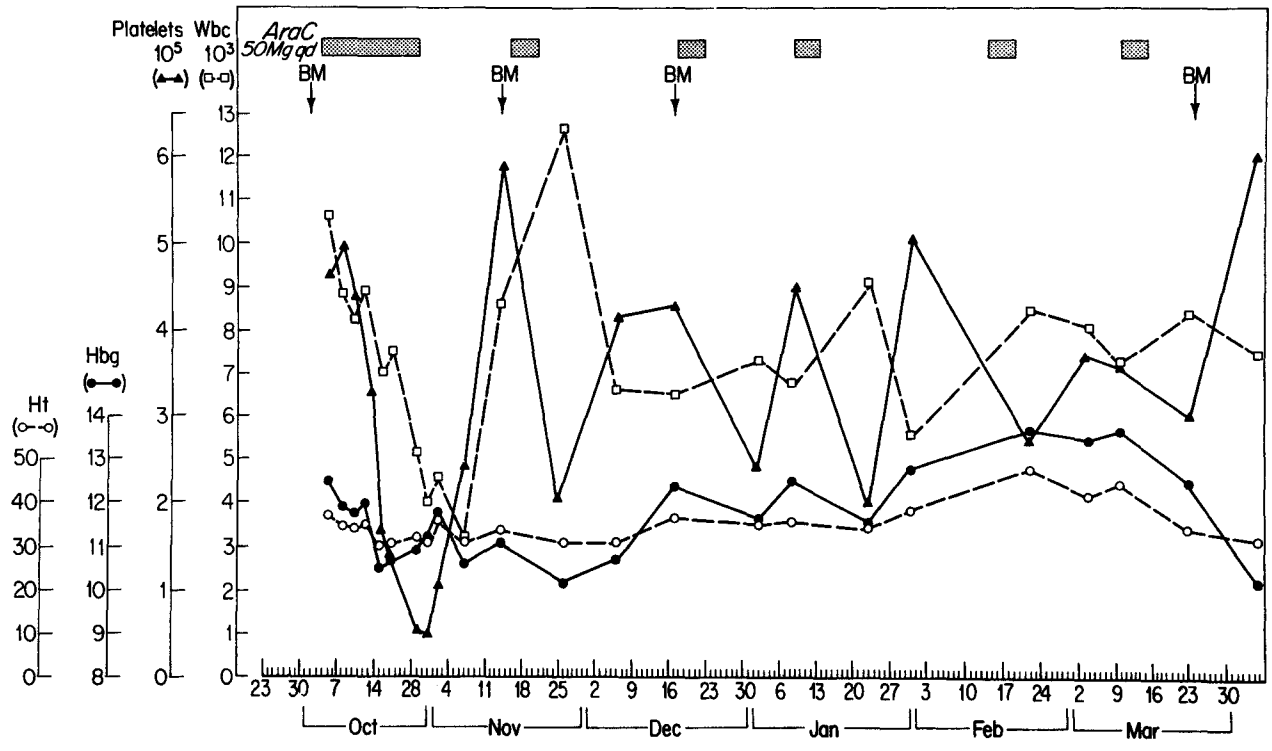

Fig. 1. Treatment of early AML with low dose Ara-C (Patient E.E.)

Case 2 (F.A.): This 43-year-old, previously well female developed over a 4 week period progressive weight loss, fever, and severe generalized intermittent bone pain. There were no positive physical findings except marked sternal tenderness. Blood studies were unremarkable except for a mild degree of anemia and a rapid E.S.R. A bone scan, carried out to detect possible metastatic cancer, showed abnormal uptake in the ribs, pelvis, and long bones. Marrow aspirate and biopsy were performed and revealed hypercellularity with a variable picture. In some areas there were sheets of myeloblasts with Auer rods noted in some cells; elsewhere the marrow was hypercellular with a shift to the left, but myeloblasts were absent. The patient experienced increased bone pain which required narcotics for relief. She was started on Ara-C 1 mg per kilogram (50 mg) daily s.c. and this was continued for 21 days. Bone pain markedly decreased after the first week of therapy and she gained weight and strength. A moderate fall in hematocrit, WBC, and platelets developed after 21 days of therapy, but following cessation of Ara-C there was a rapid rise in platelets followed by a slower increase in WBC and hematocrit to normal levels. A marrow aspirate taken two months after Ara-C was started showed an M1 marrow. The patient has regained full activities, gained 20 pounds, and is now in her 4th month of remission. Maintenance therapy consists of Ara-C 50 mg daily s.c. for five days each month (Fig. 2).

In addition to the cases of early ANLL seven other patients have been treated; three sideroblastic RDA-ANLL cases failed to respond to several courses of low dose Ara-C and four patients with RDA-ANLL have been started

Table 1. Results of Low Dose Ara-C Therapy

Category	Total Cases	Complete remission	Failure	Early	Alive	Dead
Early ANLL Sideroblastic	2	2	0	0	2	0
RDA-ANLL Nonsideroblastic	5	0	3	2	4	1
RDA-ANLL	2	0	0	2	2	0
Total	9	2	3	4	8	1

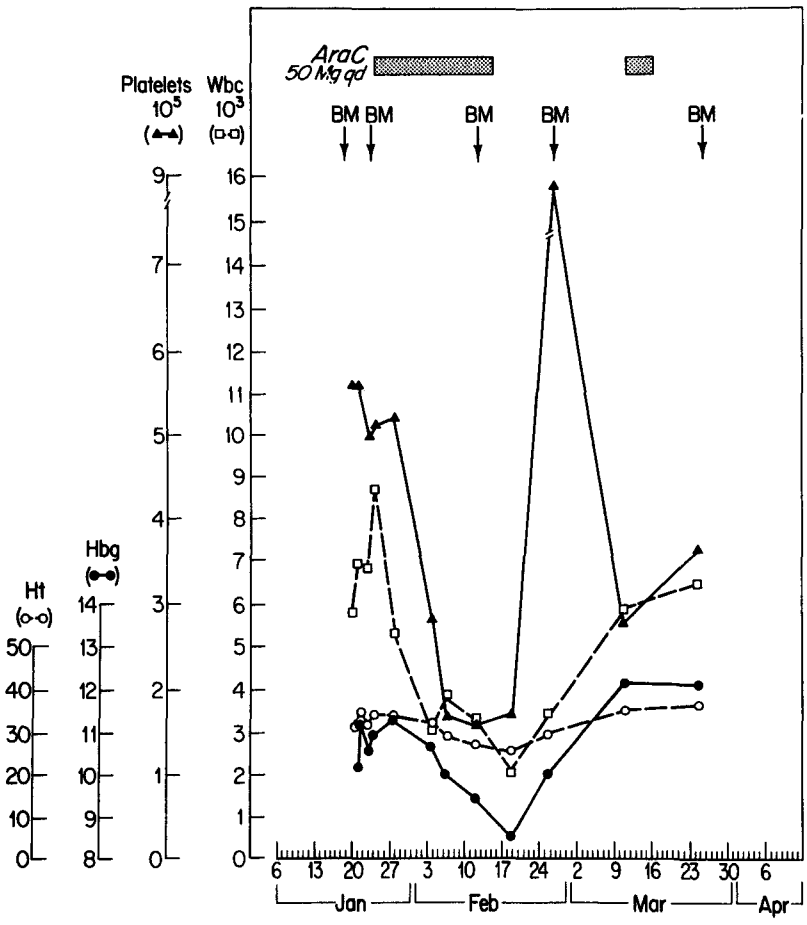

Fig. 2. Treatment of early AML with low dose Ara-C (Patient F.A.)

on therapy but it is too early to evaluate results in these cases. (See Table 1).

C. Results of diffusion Chamber Studies

Studies have been carried out over the past 5 years on the proliferation and maturation of marrow cells from patients with RDA, leukemia, and other disorders. Cells from young normal marrow donors mature and fail to proliferate; in older patients cells mature and frequently a marked lymphocytosis develops (Fig. 3). Studies on patients with RDA, early ANLL, and de novo ANLL showed that cells (1) failed to proliferate or (2) grew and matured at least to promyelocytes in all but 9% of 117 cases.

Observations of the effect of low dose Ara-C on growth and maturation of marrow cells were carried out by treating host rats with 0.1 mg per kilogram Ara-C daily s.c. for 21 days. The pretreatment marrow cells of patient F.A. with early ANLL showed a striking neutrophilocytosis on day 5 followed by an intense lymphocytosis from days 8–14. In the untreated control cultures a similar but less intense cellular response occurred (Fig. 4). In four cases of RDA-ANLL and one nonleukemic RDA an effect on maturation by low dose Ara-C was noted in two instances but was equivocal in three other patients. In one case of de novo ANLL myeloblasts proliferated actively and neither growth nor maturation was influenced by Ara-C.

D. Discussion

The successful results of low dose Ara-C therapy in two cases of early ANLL may be unique since in both cases the disease was discovered incidentally and the marrows were only partially replaced with blasts. The early stage of ANLL is more commonly encountered in cases of RDA "going over" to ANLL. Since these elderly patients have little hope of achieving remissions with present day aggressive chemotherapy, low dose Ara-C might offer an alternative form of therapy at least in some cases. Unfortunately our first three patients with sideroblastic RDA-ANLL failed to obtain remissions with low dose Ara-C and the results in four additional cases, recently started on therapy, are unavailable. However, further clinical trials should be carried out not

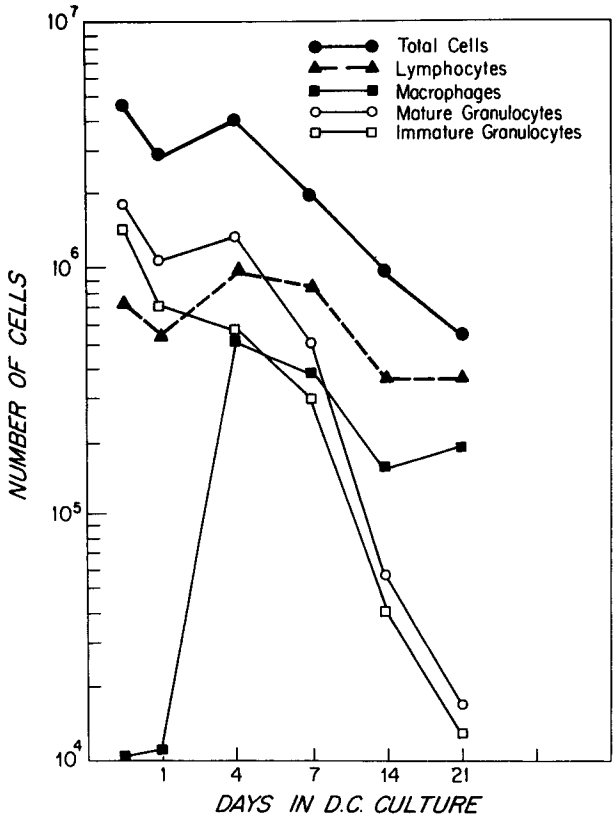

Fig. 3. Diffusion culture of bone marrow cells from 11 older adults

only with low dose Ara-C but with other antileukemic agents investigated by Sachs (1978).

It is well established that leukemic cells will differentiate in DC cultures (Hoelzer et al. 1979). Our preliminary experiments indicate that low dose Ara-C may enhance differentiation of leukemic cells in some cases of ANLL. DC culture studies may prove useful in selecting candidates for low dose Ara-C therapy and more importantly may provide a method of investigating the fundamental problems of growth and differentiation of leukemic myeloblasts in man.

References

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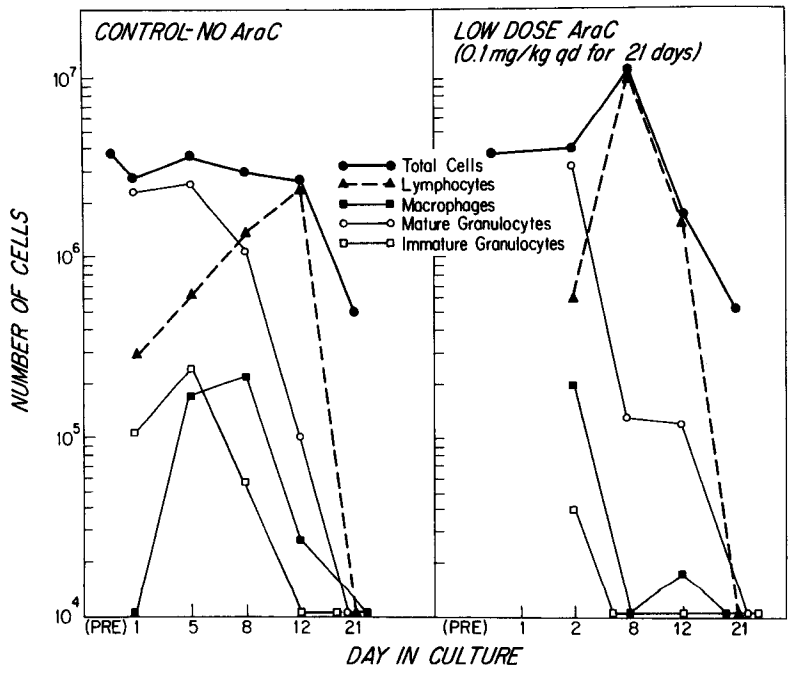

Fig. 4. Bone marrow cells in D.C. culture (Patient F.A.)