Low-Dose Cytosine Arabinoside (Ara-C) Therapy in the Myelodysplastic Syndromes and Acute Leukemia

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Twenty-two patients with either a myelodysplastic syndrome or acute nonlymphocytic leukemia were treated with 10–21 days of subcutaneous cytosine arabinoside (Ara-C) (5–10 mg/m² every 12 hours). There were two complete remissions and ten partial responses. Clinically significant improvements in peripheral blood counts persisted for periods of 8 weeks to greater than 21 weeks. Responses were seen even in patients who had previously proven refractory to conventional induction regimens or high-dose Ara-C. The toxicity, however, was considerable. Nearly all patients developed significant thrombocytopenia. Platelet and red cell transfusion support was required in many cases. The response to low-dose Ara-C therapy seen in patients with the leukemic and myelodysplastic disorders may be mediated by the induction of cell differentiation or a direct cytotoxic effect on a sensitive population of cells. Low-dose Ara-C may provide an alternative therapy in the selected patient with acute nonlymphocytic leukemia or a myelodysplastic syndrome.

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ACUTE NONLYMPHOCYTIC LEUKEMIA is characterized by an arrest in normal myeloid maturation.[1] Unable to mature beyond the myeloblast stage, the malignant leukemic cells accumulate, suppress normal hematopoiesis and thereby cause anemia, neutropenia and thrombocytopenia. Studies *in vitro* have shown that leukemic cells can be induced to differentiate beyond the stage of their maturation arrest in the presence of a variety of chemical reagents including cytosine arabinoside (Ara-C).[1-3] Since its introduction in 1965, Ara-C has been one of the most widely used and effective antileukemic agents. At conventional doses, Ara-C exerts its cytotoxic effects by inhibiting DNA replication. The mechanism by which it may promote cell differentiation at low doses, however, is unknown.

In preliminary clinical studies, treatment with low-dose Ara-C resulted in an increase in the proportion of granulated cells in the bone marrows of patients with acute undifferentiated leukemia.[4] This has been interpreted as evidence of a differentiating effect of low-dose Ara-C *in vivo* rather than a direct cytotoxic effect. Furthermore, in the early trials of low-dose Ara-C therapy, hematologic improvement was observed in patients with acute leukemia and the closely related preleukemic (myelodysplastic) syndromes.[5,6] Elderly and chronically ill patients tolerate intensive chemotherapy poorly. Therefore, to assess further both the efficacy and toxicity of low-dose Ara-C therapy as an alternative approach to the treatment of selected patients, we treated 22 patients with either a myelodysplastic syndrome or acute nonlymphocytic leukemia.

Patients and Methods

Patient Population

Twenty-two patients with either a myelodysplastic syndrome or acute nonlymphocytic leukemia were treated with subcutaneous low-dose Ara-C at three institutions (Northwestern University, The University of Chicago, and Tufts-New England Medical Center) between October 1981, and September 1983. The median

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TABLE 1. Response to Low-Dose Ara-C

Disease	No. of patients	No. of responses	Duration of response (Wks)
Myelodysplastic Syndromes			
Refractory anemia	1	0	
Chronic myelomonocytic leukemia	2	1	17
Refractory anemia with excess blasts	1	0	
Refractory anemia with excess blasts in transformation	6	4	1,* 8, 12, 13
Acute Nonlymphocytic Leukemia			
Untreated, de novo	2	2	11, 15,†
Previously treated	4	1	21
Post-myelodysplastic syndrome or CML in blast phase	6	4	4,‡ 13, 16+,† 17
Totals	22	12	

* Patient expired on day 28, of an intracerebral bleed.
† Complete response.
‡ Patient died of sepsis on day 55.
CML: chronic myelogenous leukemia.

age was 70 years (range, 26–80); there were 11 males and 11 females.

These patients constituted the following three groups: (1) individuals with a myelodysplastic syndrome as defined and subclassified by the French-American-British Cooperative Group;[7] (2) patients older than age 70 years with acute nonlymphocytic leukemia *de novo;* and (3) patients with refractory or relapsed acute leukemia following conventional chemotherapy.

Ten patients had a myelodysplastic syndrome (Table 1); four of the five subcategories currently defined were represented. There was one patient with refractory anemia, two with chronic myelomonocytic leukemia, one with refractory anemia with excess blasts (5%–20% blasts), and six with refractory anemia with excess blasts in transformation (20%–30% blasts). Although no patient with sideroblastic anemia *per se* was entered, two patients with refractory anemia with excess blasts in transformation had ringed sideroblasts in the bone marrow at the time of diagnosis as did one patient with acute leukemia. To be eligible for treatment with low-dose Ara-C, patients with myelodysplastic syndromes were required to manifest cytopenias involving at least two of three hematopoietic cell lines.

A total of 12 patients had acute nonlymphocytic leukemia. This included three elderly patients with previously untreated acute leukemia. Four other patients had received prior treatment for acute leukemia; two entered this study after proving refractory to initial therapy and two entered at the time of first relapse. Also included were five patients who developed acute leukemia after a previous myelodysplastic syndrome or chronic myelogenous leukemia. Three of these five had received intensive cytotoxic therapy for acute leukemia prior to their treatment with low-dose Ara-C.

Treatment Regimen

Ara-C was administered as a subcutaneous injection. Individuals capable of self-injection were monitored carefully as outpatients. Twenty patients were treated with Ara-C 10 mg/m^2 subcutaneously every 12 hours. Sixteen of these patients received a full 21-day course of therapy; in four cases, treatment was discontinued by the patient's personal physician after only 10 to 14 days of therapy because of falling platelet counts. An additional two patients were treated with Ara-C 5 mg/m^2 subcutaneously every 12 hours for 10 and 14 days. Individuals who did not respond to a single course of low-dose Ara-C were removed from the study.

Criteria for Response

The response to therapy was assessed by both bone marrow examination and peripheral blood counts. Complete remission was defined as a normal hemogram and fewer than 5% blasts in a bone marrow which was at least 25% cellular. The following criteria for partial response were employed: (1) a decrease in the monthly red blood cell transfusion requirement by 50%; (2) an increase in the hemoglobin by 2 g/dl; (3) an increase in the platelet count by 30,000/ul in patients with pretreatment thrombocytopenia; (4) an increase in the neutrophil count by 1000/ul in patients with pretreatment neutropenia; or (5) a decrease in the percentage of blasts in the bone marrow by 50% in patients with refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or acute leukemia. Partial responses noted in the peripheral blood only (criteria 1–4) were documented on at least three occasions over a minimum period of 8 weeks.

Results

Twenty-two patients were treated with low-dose Ara-C, and 12 responded. There were two complete remissions and ten partial responses. The distribution of patients according to disease entity and response is listed in Table 1. With seven exceptions, patients were able to self-administer Ara-C at home.

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TABLE 2. Characteristics of Response to Low-Dose Ara-C Therapy

	Bone Marrow				Peripheral Blood			
Case no.	% Blasts Pre(Post)	% Mature WBCs* Pre(Post)	% Erythroids Pre(Post)	Megas (Post)	Hgb (g/dl) Pre(Post)	PMNs/ul Pre(Post)	% Blasts Pre(Post)	Platelets ($\times 10^9$/l) Pre(Post)
1	82 (3)	1 (27)	1 (45)	↑	7.5(14.9)	1406 (5002)	8 (0)	63 (185)
2	18 (6)	NC	NC	↑	11.9 (14.6)	99 (3248)	4 (0)	60 (164)
3	NR	NR	NR	NR	9.2 (14.2)	NC	25 (0)	NC
4	NR	NR	NR	NR	†	NR	NR	NC
5	32 (0)	2 (83)	NR	NR	NR	NR	NR	NR
6	95 (30)	5 (34)	0 (28)	↑	7.5 (14.2)	NC	NC	54 (141)
7	15 (1)	2 (54)	NR	NR	NR	NR	9 (1)	NR
8	20 (14)	NR	3 (15)	↑	NR	NC	15 (0)	74 (205)
9	25 (14)	5 (29)	20 (43)	NC	7.7 (11.3)	76 (2254)	3 (0)	10 (232)
10	NC	3 (18)	0 (10)	↑	NR	NR	NR	32 (260)
11	31 (2)	10 (45)	15 (40)	↑	7.2 (11.4)	741 (2928)	2 (0)	NC
12	20 (2)	8 (27)	49 (59)	↑	NC	NR	7 (0)	22 (94)

* Percentage of metamyelocytes, band forms, and polymorphonuclear leukocytes.

† Decreased transfusion requirement.

Megas: megakaryocytes; NC: no change from the pretreatment values which were normal; NR: no response.

Five of 10 patients with a myelodysplastic syndrome manifested partial responses. Improvements in the hemogram were observed for periods of 8 to 17 weeks. One patient with refractory anemia with excess blasts in transformation had evidence of a response to Ara-C by bone marrow examination on day 21, but died of an intracerebral hemorrhage on day 28, prior to recovery of her peripheral blood counts. Only one patient who responded received maintenance therapy (Ara-C 10 mg/m^2 subcutaneously every 12 hours for 1 week per month). Of interest, the duration of his response was the longest at 17 weeks.

Twelve patients with acute nonlymphocytic leukemia were treated with low-dose Ara-C; two had complete remissions and five had partial responses. Improvements in peripheral blood counts persisted for 11 to 21+ weeks. Two patients with previously untreated acute leukemia *de novo* demonstrated a response to therapy, whereas only one of the four previously treated or refractory acute leukemic patients responded. Prior therapy for these four patients consisted of conventional dose Ara-C and an anthracycline. One patient also received high-dose Ara-C. Four patients whose acute leukemia evolved from a prior myelodysplastic syndrome or chronic myelogenous leukemia demonstrated a response to this treatment; two of these responders had previously received cytotoxic therapy for acute leukemia. Two patients with acute leukemia who had previously received conventional dose Ara-C and one who had received high-dose Ara-C (3 g/m^2 intravenously twice daily) demonstrated responses to low-dose Ara-C. Maintenance low-dose Ara-C therapy was administered to only one of the acute leukemic patients who responded, and the duration of his response was 13 weeks.

Whereas 11 of the 16 patients who received a full 21-day course of Ara-C at 10 mg/m^2 every 12 hours responded, only one of four who received 10–14 days at the same dose did. Neither patient who received Ara-C 5 mg/m^2 for 10 or 14 days benefited from therapy.

At the time of progression, two responders with acute leukemia and two with myelodysplastic syndromes were retreated, but none responded.

The M1, M2, and M4 subtypes of acute nonlymphocytic leukemia were represented in our sample. The numbers are too few to draw any conclusions regarding the sensitivity of an individual subclass to low-dose Ara-C therapy.

Character of Response

Responses were heterogeneous in character as demonstrated in Table 2. Clinically significant improvements in hemoglobin concentration or peripheral neutrophil or platelet counts were seen in 10 of 12 responders. Two patients (Cases 1 and 11) fulfilled criteria for a complete remission. The remainder of responses were partial and persisted for as long as 5 months. Figure 1 illustrates the peripheral response seen in a patient with refractory anemia with excess blasts in transformation (Case 9).

Despite striking evidence of a response in the bone marrow (Figs. 2A–2C), peripheral blood counts remained unchanged in one patient (Case 5) with acute leukemia and a prior history of Philadelphia chromosome-negative chronic myelogenous leukemia with trisomy 8. Whereas the pretreatment marrow examination showed mostly blasts and promyelocytes, the post-therapy aspirate revealed a predominance of metamyelocytes, band forms and polymorphonuclear leukocytes. The mature myeloid cells in the posttreatment bone marrow, however, were morphologically abnormal with very clumped chromatin and a Pelger-Huet-like appearance characteristic of the patient's chronic phase granulocytes.

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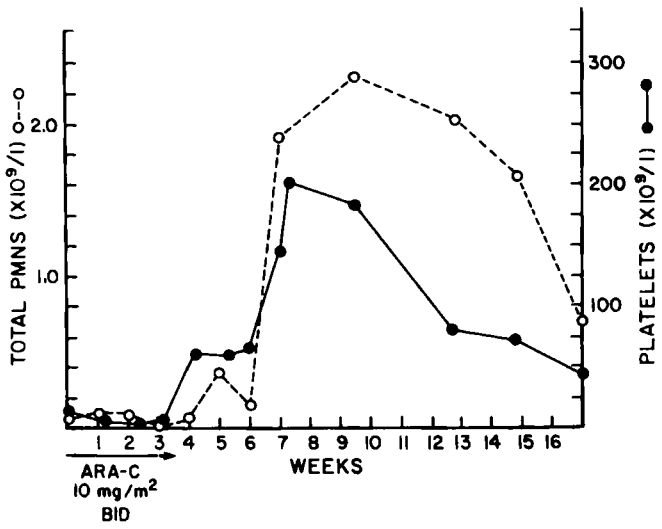


FIG. 1. The polymorphonuclear (PMN) leukocyte and platelet counts of a patient with refractory anemia with excess blasts in transformation treated with low-dose Ara-C (Case 9).

Two patients had no visible change on bone marrow examination but, nonetheless, had either a sustained rise in hemoglobin or a fall in transfusion requirement.

The gradual nature of the response to low-dose Ara-C therapy observed in some patients is best exemplified by Case 11, one of the two complete responders (Figs. 3A and 3B). This patient first presented with anemia and neutropenia. The pretreatment bone marrow examination showed acute nonlymphocytic leukemia with moderate dysplastic changes suggestive of a prior myelodysplastic syndrome. The cytogenetic examination was normal. She received Ara-C 10 mg/m^2 subcutaneously every 12 hours for 21 days, and became pancytopenic. A repeat bone marrow examination performed during therapy on day 14, showed a moderately hypocellular marrow, otherwise unchanged from the pretherapy specimen. On day 28, a bone marrow examination was suggestive of a mild increase in the numbers of mature myeloid forms. Her peripheral counts began to rise in the seventh week. By day 108, her neutrophils exceeded 1500/ul. It was not until day 142, that the peripheral blood counts were normal, and a bone marrow aspirate and biopsy showed evidence of a complete remission. In contrast, the second patient with a complete response, Case 1, had a more rapid response to therapy and met criteria for a complete remission by day 42.

A moderate decline in marrow cellularity was noted

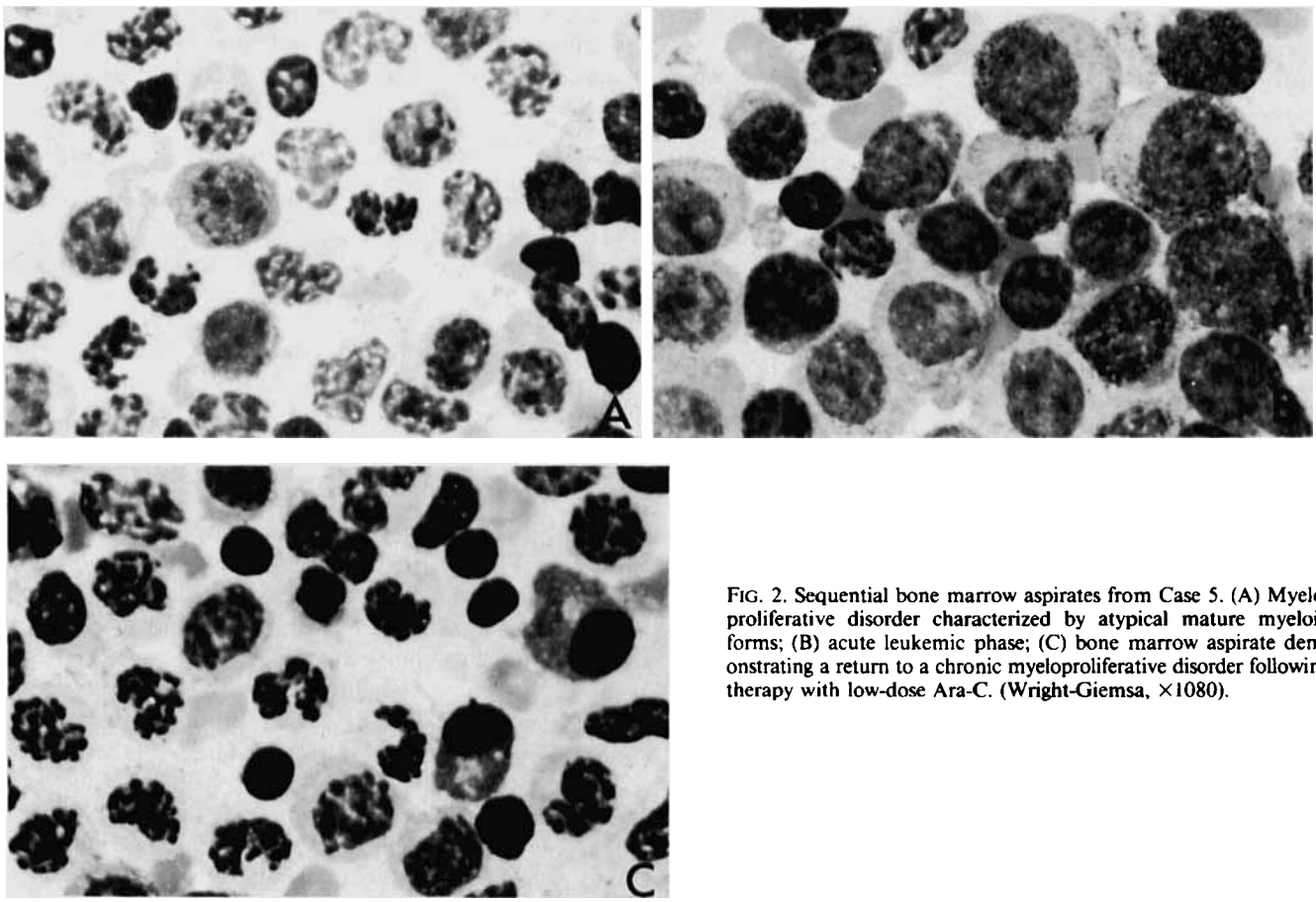
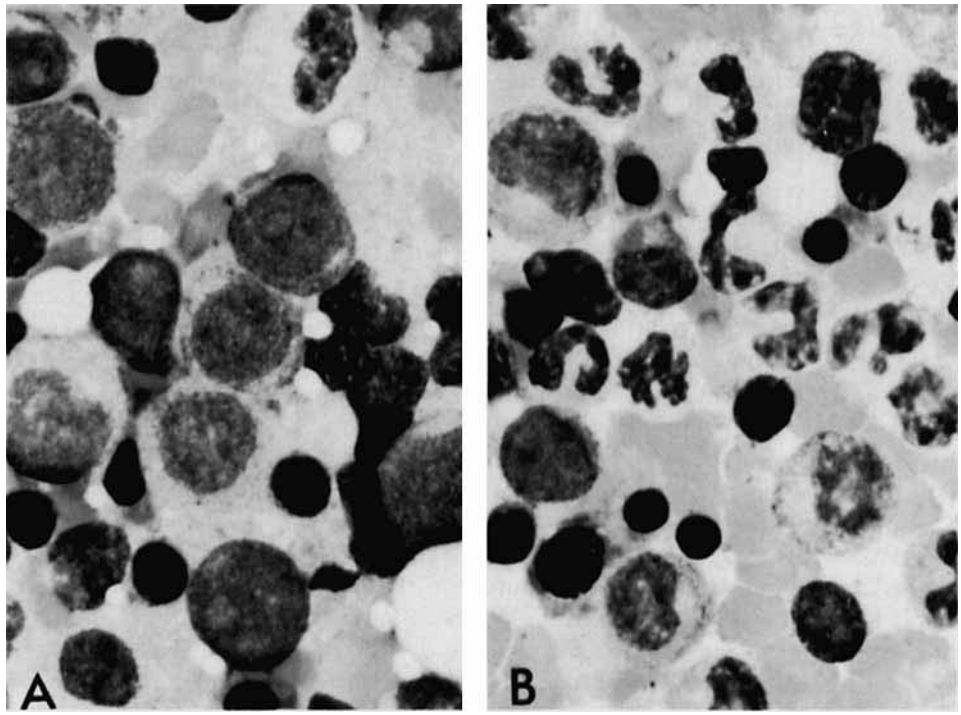


FIG. 2. Sequential bone marrow aspirates from Case 5. (A) Myeloproliferative disorder characterized by atypical mature myeloid forms; (B) acute leukemic phase; (C) bone marrow aspirate demonstrating a return to a chronic myeloproliferative disorder following therapy with low-dose Ara-C. (Wright-Giemsa, ×1080).

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FIGS. 3A AND 3B. Bone marrow aspirates from Case 11. (A) Acute nonlymphocytic leukemia; (B) mature myeloid cells in a normal appearing bone marrow following low-dose Ara-C therapy (Wright-Giemsa, ×1080).

in the majority of responders when the marrow was rebiopsied after low-dose Ara-C. However, two responders continued to demonstrate hypercellularity, suggesting that a beneficial response to low-dose Ara-C therapy may not require a period of marrow hypoplasia: Cases 5 and 7 demonstrated improvements in the degree of maturation in their bone marrows without undergoing a period of marrow hypocellularity. None of the nonresponders had a fall in cellularity following treatment.

Toxicity

Treatment-related thrombocytopenia occurred in 17 cases and was serious (<20,000/ul) in nine, resulting in one fatal intracerebral hemorrhage and one upper gastrointestinal bleed (Fig. 4). The median time to the development of serious thrombocytopenia was 11 days (range, 6–21) with recovery occurring by day 35 (range, 28–42) in the majority of cases. The development of treatment-related thrombocytopenia was independent of the duration of therapy or pretreatment platelet count.

Treatment-related neutropenia (<500 neutrophils/ul) occurred in five patients, and fever which required antibiotics occurred in nine. The majority of patients required red blood cell transfusions for symptomatic anemia during therapy. Of the 15 patients who received treatment as outpatients, 8 required admission for transfusion, fever or hemorrhage.

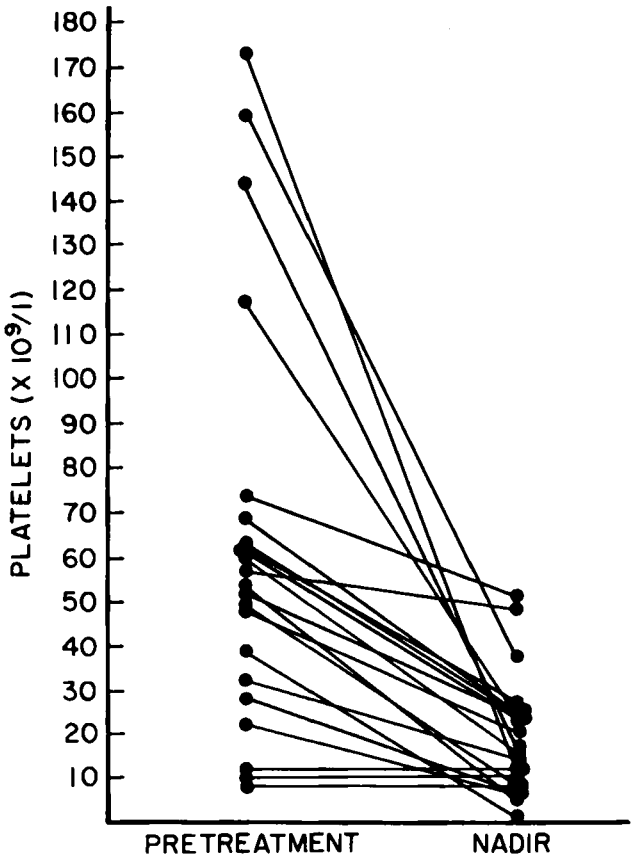


FIG. 4. Pretreatment and nadir platelet counts in 22 patients treated with low-dose Ara-C.

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Cytogenetic Analysis

Cytogenetic analyses utilizing banding techniques were performed on 19 of the 22 patients prior to low-dose Ara-C therapy. Eleven patients had abnormal karyotypes. The presence of abnormal metaphase cells with or without the persistence of normal cells did not correlate with response. No single cytogenetic abnormality had predictive value. Both complete responders had normal karyotypes prior to therapy.

Discussion

We initiated this multi-institutional trial of subcutaneous Ara-C therapy to evaluate preliminary reports that low-dose Ara-C may be beneficial in the treatment of acute leukemia and myelodysplastic syndromes. Complete responses were observed in 2 and partial responses in 10 of 22 such patients treated with 5 to 10 mg/m^2 subcutaneously, every 12 hours, for 10 to 21 days. Responses were heterogeneous in character, but clinical improvement resulted for periods of from 8 weeks to greater than 21 weeks. Even patients whose disease had previously proven refractory to conventional cytotoxic agents or high dose Ara-C benefited from treatment. These findings support earlier observations that low-dose Ara-C can produce clinically meaningful respones in patients with preleukemic syndromes or acute nonlymphocytic leukemia. The low-dose Ara-C therapy was easily administered, and 15 patients capable of self-injection were treated as outpatients. In contrast to reports by other investigators, toxicity was frequent with the majority of patients developing thrombocytopenia by the second week. Fever, requiring hospital admission and antibiotics, was also common. Intensive platelet and red blood cell transfusion support was a necessity.

A single 24-hour intravenous infusion of low-dose Ara-C has been reported to result in an increase in the percentage of granulated cells in the bone marrows of patients with acute undifferentiated leukemia.[4] These findings have been interpreted as evidence of the maturing effects of Ara-C on leukemic blasts. Complete remissions have been reported in three patients with acute leukemia treated with low-dose Ara-C.[5] The gradual rise in peripheral blood counts has been regarded as supportive evidence that Ara-C in low doses acts to induce cell differentiation rather than cell death. These preliminary results have been confirmed in additional patients.[6,8] In contrast to the experience reported here, other investigators have encountered little toxicity. The reasons for the marked differences in reported side effects and complications is unclear but may reflect the patient population or study design.

Like acute nonlymphocytic leukemia, the myelodysplastic syndromes are characterized by an established malignant clone and defective cell maturation.[9] Low-dose Ara-C therapy of patients with these disorders, like the treatment of patients with acute leukemia, has produced both partial and complete remissions.[8,10] The relative response rates for the individual subytpes of the myelodysplastic syndromes will need to be defined in larger stratified studies.

The mechanism by which low-dose Ara-C effects responses in patients with acute leukemia and the closely related preleukemic syndromes is unclear. While *in vitro* evidence suggests that Ara-C may act as a differentiating agent, its *in vivo* effect may be on the basis of more than one mechanism. Our data suggest several possibilities. The character of the response seen in the patient in Case 5, an elderly woman with acute leukemia preceded by a smoldering leukemic process, can be interpreted as support for the differentiating effect of Ara-C. The chronic phase of this patient's disease was characterized by very distinctive Pelger-Huet-like abnormalities in the mature myeloid cells (Fig. 2A). When the disease accelerated, leukemic myeloblasts predominated (Fig. 2B). At the completion of low-dose Ara-C therapy the bone marrow, although still hypercellular, was virtually repopulated with mature myeloid cells, all of which shared the same abnormalities characteristic of her chronic phase neutrophils (Fig. 2C). Assuming the presence of only a single clone of malignant cells, it is conceivable that low-dose Ara-C caused the malignant myeloblasts to differentiate into these distinctive abnormal granulocytes. Further studies using cytogenetic, isoenzyme, or other markers to identify the mature myeloid cells in the remission bone marrow as the differentiated progeny of the pretreatment myeloblasts will be required to document a differentiating effect of low-dose Ara-C.

Alternatively, it is possible that even at these very low doses, Ara-C exerts a cytotoxic effect. At low concentrations, Ara-C may be sufficiently cytotoxic to rid the marrow of a very susceptible leukemic clone, but not toxic enough to prevent regeneration of normal hematopoietic elements. It has been reported that the addition of leukemic blasts to cultures of normal cells containing low concentrations of Ara-C reduces the cytotoxic effect of the drug on the normal cells.[11] This phenomenon may explain the bone marrow's apparent ability to regenerate during low-dose Ara-C treatment. The moderate decline in bone marrow cellularity seen in the majority of our reponders following low-dose Ara-C therapy is presumably due to a cytotoxic effect. A brief period of hypoplasia may have gone undetected in the two patients in whom the cellularity appeared to be

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unchanged. However, none of our patients developed aplasia, suggesting a moderate or selective cytotoxicity.

In some patients, Ara-C may cause partial responses by inhibiting a suppressive effect of the leukemic clone on normal progenitors. Leukemic blasts may indirectly suppress normal hematopoiesis.[12] These inhibitors of normal progenitor cells may account for many of the clinical features of the myelodysplastic syndromes. Ara-C may directly effect these abnormal regulators of hematopoiesis without completely eliminating the myeloblasts from the bone marrow.

Treatment with low-dose Ara-C has rapidly come into vogue among hematologists. Although this therapy can be administered on an out-patient basis in many patients, our data suggests that it is not without toxicity and uniformly results in severe thrombocytopenia. Furthermore, the optimal dose and duration of treatment remains to be determined. Only two of our responses were complete, and the majority were of short duration. Large, stratified multi-institutional studies will be required to determine the subgroup of patients for which this is appropriate therapy. A randomized ECOG trial of low-dose Ara-C therapy versus supportive therapy alone in the myelodysplastic syndromes is underway and will help establish the degree to which patients with the preleukemic disorders benefit from this therapy. Treatment with low-dose Ara-C may provide the basis for innovative, alternative therapy for high risk patients with a myelodysplastic syndrome or acute nonlymphocytic leukemia. Correlative *in vitro* investigations may help elucidate the mechanism by which low-dose Ara-C induces remission.

REFERENCES

1. Koeffler HP. Induction of differentiation of human acute myelogenous leukemia cells: Therapeutic implications. *Blood* 1983; 62: 709.

2. Lotem J, Sachs L. Different blocks in the differentiation of myeloid leukemic cells. *Proc Natl Acad Sci USA* 1974; 71:3507.

3. Griffin J, Munroe D, Major P, Kufe D. Induction of differentiation of human myeloid leukemia cells by inhibitors of DNA synthesis. *Exp Hematol* 1982; 10:774.

4. Baccarani M, Tura S. Differentiation of myeloid leukemic cells. *Br. J Haematol* 1979; 42:485.

5. Housset M, Daniel MT, Degos L. Small doses of Ara-C in the treatment of acute myeloid leukemia cells? *Br J Haematol* 1982; 51: 125.

6. Moloney WC, Rosenthal DS. Treatment of early acute nonlymphatic leukemia with low-dose cytosine arabinoside. In Neth R, Gallo RC, Graf T, Mannweiler K, Winkler K, eds. Modern Trends in Human Leukemia. IV. Berlin: Springer-Verlag, 1982; 59.

7. Bennett JM, Catovsky D, Daniel MT *et al.* Proposal for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; 51:189.

8. Castaigne S, Daniel MT, Tilly H, Herait P, Degos L. Does treatment with Ara-C in low dosage cause differentiation of leukemic cells? *Blood* 1983; 62:85.

9. Koeffler HP, Golde DW. Human preleukemia. *Ann Intern Med* 1980; 93.

10. Wisch JS, Griffin JD, Kufe DW. Response of preleukemic syndromes to continuous infusion of low-dose cytarabine. *N Engl J Med* 1983; 309:1599.

11. Gordon MY, Douglas DC, Blackett NM. Effect of medium conditioned by acute myeloid leukemia cells on normal marrow colony-forming ability and sensitivity to cytosine arabinoside. *Eur J Cancer* 1978; 14:661.

12. Broxmeyer HE, Bognacki J, Dorner MH, de Sousa M. Identification of leukemia-associated inhibitory activity as acidic isoferritins. *J Exp Med* 1981; 153:1426.

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