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Limited efficacy of a four-day course of high-dose cytosine arabinoside in the treatment of poor-risk patients with acute nonlymphocytic leukemia*

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Summary. High-dose cytosine arabinoside therapy was administered to 29 patients with poor-prognosis acute nonlymphocytic leukemia. In an attempt to reduce toxicity, therapy was divided into an initial 4-day course of therapy, followed by a 3-day course if the marrow aspirate examined 1 week after the end of treatment contained substantial numbers of leukemic cells. Of the 29 patients, 5 entered complete remission, 2 of them after the initial 4-day course of therapy. The toxicity of split-course therapy was the same as that of conventional 6-day high-dose cytosine arabinoside therapy. This study demonstrates that the modification of high-dose cytosine arabinsoide therapy used in this study failed to reduce toxicity and produced a lower remission rate than that obtained with the 6-day course of therapy.

Introduction

The introduction of single-agent high-dose cytosine arabinoside remission induction therapy (HDaraC) [2, 3, 5] for the treatment of acute nonlymphocytic leukemia (ANLL) [1] offered the possibility of an effective remission induction regimen which would be free of anthracycline-associated cardiac toxicity. Unfortunately, the most commonly used dose and schedule (3 g/m^2 every 12 h for 6 days) proved to be associated with cerebellar toxicity [9]. In an attempt to reduce this serious side-effect we initiated a pilot study for the treatment of poor-risk ANLL patients, in which the dosage of cytosine arabinoside was reduced by one-third and the treatment schedule altered so that patients with highly responsive leukemia could be treated with 8 doses of drug instead of the usual 12 doses.

Material and methods

Patients were eligible for treatment if they had newly diagnosed ANLL [1] and were at high risk of failing remission induction therapy with cytosine arabinoside/anthracycline antibiotic because they were over 70 years of age or because their leukemia either developed after exposure to marrow toxins or appeared subsequent to a preleukemic state [8].

In an attempt to reduce the overall toxicity of the conventional 6-day high-dose cytosine arabinoside regimen [9], remission induction therapy was 'split' into an initial 4-day course of therapy followed by a 1-week rest period, with the remainder of therapy (3 additional days) administered if the day-11 bone marrow aspirate contained a significant number of leukemic cells. The bone marrow leukemic cell mass was calculated by multiplying the percentage of leukemic cells in the marrow aspirate with the percentage biopsy cellularity [10].

Cytosine arabinoside was administered every 12 h as a 75-min infusion for eight doses. The second part of therapy consisted of six doses and was administered on days 11, 12, and 13 if the bone marrow on day 11 contained 20% leukemic cells or more. Most patients (25) received the cytosine arabinoside at 2 g/m^2, 3 patients, at 3 g/m^2, and 1 was treated at 1 g/m^2. All patients received treatment with steroid-containing eye drops while receiving therapy. Complete remission was defined as a return of hematopoiesis to normal without evidence of the signs or symptoms of leukemia [8]. For a complete remission to have been obtained the bone marrow had to be normocellular, with normal erythropoiesis, myelopoiesis, and thrombopoiesis without evidence of residual leukemic cells. The peripheral blood had to contain 1500 or more granulocytes/μl, and 100 000 or more platelets/μl. A system was used to define the types of treatment failures [8]. This system of classification was sightly modified from our original proposal [7]. Toxicity was classified using the criteria proposed by the Eastern Cooperative Oncology Group [6].

Results

Of the 29 patients treated, 15 were 70 years of age or older, while 14 patients were under 70 years. Among the former patients, 4 had a history of a myelodysplastic or myeloproliferative disorder prior to the appearance of acute leukemia and 1 patient had a history of exposure to known hematopoietic toxins in the past. Among the 14 patients less than 70 years of age, 8 had a history of exposure to known hematopoietic toxins, while 6 had had a myelodysplastic syndrome of unknown origin. A detailed presentation of these data can be found in Table 1.

Of the 29 patients, 5 (17%) entered complete remission, 10 (34%) failed treatment because of persistent leukemia, 12 (41%) died during therapy, and 2 patients (7%) were inevaluable. Only 2 of the 29 patients treated entered complete remission after a 4-day course of therapy. A total of

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Table 1. Patient data and outcome of treatment in each

Patient no.	Age	High-risk factor	Ps[b]	Treatment outcome[c] [9]			Survival (days)
				FAB	Course 1	Course 2	
1	70	Age	1	m1	REDR	REDR	30
2	74	Age	3	AUL	REDR	NDQT	17
3	80	Age	3	m4	SDR	NDQT	24
4	79	Age	3	m4	Inevaluable[f]	–	46
5	84	Age	2	m4	SDR	CR	9 months
6	76	Age	1	m2	SDR	SDR	4+ months
7	70	Age	1	m2	REDR	MHYP	34
8	74	Age	4	m2	REDR	MHYP	24
9	73	Age	3	meg. l.[d]	MHYP	–	31
10	75	Age; history thrombocythemia	1	m1	SDR	–	5+months
11	82	Age; history MDS[a]	4	m4	NDQT	–	10
12	70	Age; prior toxic exposure	1	m4	MHYP	–	11
13	71	Age; history MDS	2	m2	SDR	–	–
14	74	Age; history MDS	1	m2	REDR	CR	1+years
15	75	Age	2	m2	SDR	SDR	5 months
16	63	History MDS	3	m6	ineval.	–	12
17	68	History MDS	1	m1	SDR	MHYP	54
18	65	Prior toxic exposure	3	m6	SDR	MHYP	24
19	65	Prior toxic exposure	3	Unknown	NDQT	–	7
20	49	Prior toxic exposure	1	m2	SDR	SDR	32
21	49	History MDS	1	m4	SDR	SDR	1+years
22	62	History MDS	1	m4	REDR	MHYP	–
23	59	Prior toxic exposure	4	m4	MHYP	–	20
24	44	Prior toxic exposure	1	RAEB[e]	CR	–	10+months
25	29	Prior toxic exposure	0	m2	REDR	CR	5+months
26	65	Prior toxic exposure	4	m5	CR	–	5+months
27	58	History myelofibrosis	0	m5	REDR	REDR	6+months
28	60	History of MDS	1	m4	SDR	–	42
29	65	Prior toxic exposure	4	m6	SDR	–	35

[a] Myelodysplastic syndrome
[b] Performance status: 0 = fully active, 1 = ambulatory, capable of light work, 2 = in bed <50% of time, 3 = in bed >50% of time, capable of only limited self care, 4 = completely bedridden
[c] Treatment outcome: SDR = patient survived >7 days after end of treatment with persistence of leukemia; REDR = marrow rendered severely hypocellular but leukemic cells repopulated the marrow; NDQT = pt expired <7 days after the end of therapy; MHYP = pt expired with severely hypoplastic marrow
[d] Acute megakaryocytic leukemia
[e] Refractory anemia with excess blasts in transformation
[f] Received only one dose of drug

16 patients received the later 3-day course of therapy, and 3 of these patients entered complete remission.

Figure 1 provides information on the pretherapy bone marrow leukemic cell mass, the marrow leukemic cell mass after 4 days of therapy (8 doses), and the percentage reduction in marrow leukemic cell mass produced by therapy. For means of comparison similar data are provided for 'high-risk' ANLL patients treated with a 6-day course of therapy (12 doses) [11]. The initial leukemic cell mass was similar for patients treated in the present study and for the historical controls, with a wide range of individual values. Note that 4 days of therapy produced a median reduction in leukemic cell mass of 70%, while a 6-day course of therapy produced a median reduction of 99%.

Toxicity data are provided in Table 2. A wide variety of toxicities occurred, including stomatitis, diarrhea, and pulmonary toxicity. It should be especially noted that 21% of patients experienced some degree of cerebellar toxicity. Infection and respiratory failure were the most common causes of death, the former being associated with 13 deaths and the latter with 8 deaths. Heart failure and renal failure were associated with 3 deaths each, and the cause of death was unknown in 4 instances. Three patients died of hemorrhage. In 12 patients death was associated with two of the previously mentioned causes (e.g., infection plus respiratory failure). At the time of writing, 7 patients remain alive at 4+ months to 1+ year.

Discussion

In the study reported here an attempt was made to increase the efficacy of high-dose cytosine arabinoside therapy by reducing toxicity. This was to be accomplished by reducing both the number of doses administered from 12 to 8 and by reducing the dose administered from 3 g/m^2 to 2 g/m^2. Provision was made for patients to receive further treatment if their marrow demonstrated significant residual leukemia 1 week after the cessation of therapy. Unfortunately, only 17% of patients entered complete remission, while 41% of patients died during therapy.

While a concurrent control group is not available for comparison, data are available for 67 similar high-risk pa-

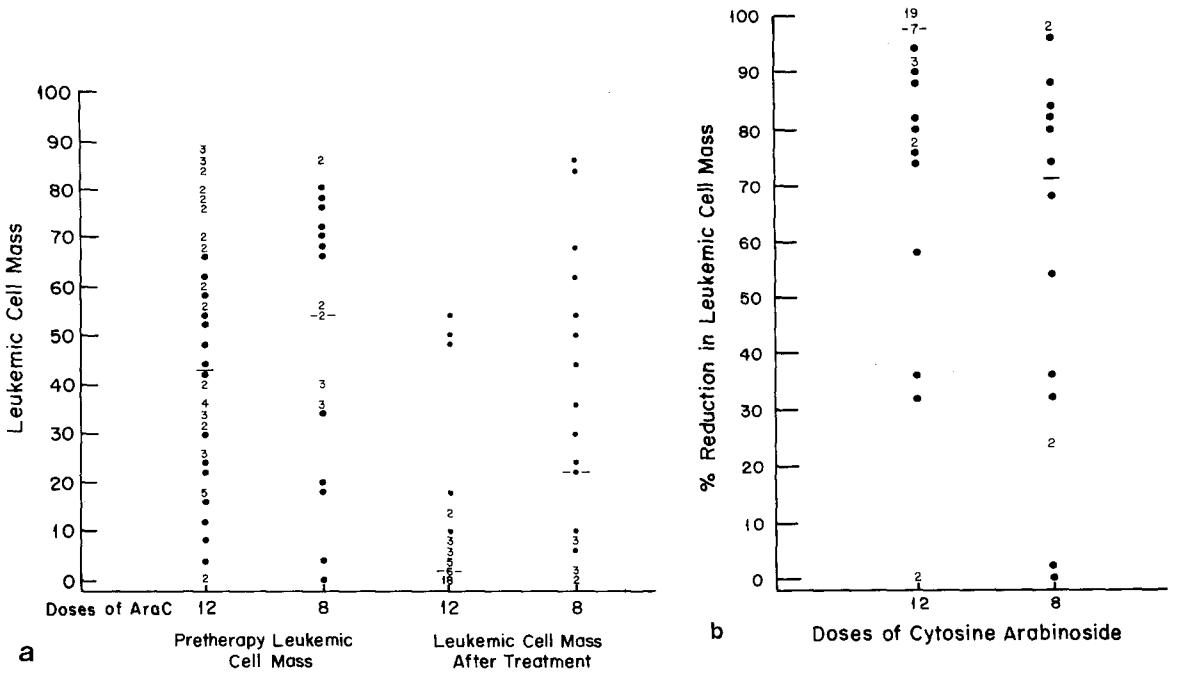

Fig. 1. Comparison of the effects of 8 doses and 12 doses of cytosine arabinoside on bone marrow leukemic cell mass (LCM). **(a)** Effect of 8 and 12 doses of araC on pretherapy LCM and LCM12 h after the last dose of drug; **(b)** percentage reduction in LCM produced by 8 and 12 doses of drug

Table 2. Toxicity

	None %	Mild %	Moderate %	Severe %	L. T. %	Lethal %
Hemorrhage	65.5	20.7	10.3	0.0	3.4	0.0
Fever w/o infection	61.5	15.4	19.2	3.8	0.0	0.0
Infection	39.3	21.4	10.7	14.3	7.1	7.1
Genitourinary	72.4	17.4	3.4	0.0	3.4	3.4
Hepatic	86.2	10.3	3.4	0.0	0.0	0.0
Nausea and vomiting	17.9	42.9	35.7	3.6	0.0	0.0
Diarrhea	55.2	27.6	17.2	0.0	0.0	0.0
Stomatitis	79.3	20.7	0.0	0.0	0.0	0.0
Pulmonary	75.0	3.6	7.1	7.1	7.1	0.0
Cardiac	86.2	3.4	3.4	3.4	0.0	3.4
Neurologic, CNS	79.3	13.8	3.4	3.4	0.0	0.0
Neurologic, PNS	93.1	3.4	3.4	0.0	0.0	0.0
Skin	77.8	14.8	7.4	0.0	0.0	0.0
Iritis	96.6	3.4	0.0	0.0	0.0	0.0
Allergy	100.0	0.0	0.0	0.0	0.0	0.0
Local toxicity	100.0	0.0	0.0	0.0	0.0	0.0
Other toxicities	89.3	3.6	3.6	3.6	0.0	0.0

tients treated with the standard 12-dose regimen [10]. Of the 67 patients, 33 were 70 years of age or older, while 23 were under 70 years of age but were in the high-risk category because of exposure to known hematopoetic toxins and/or the presence of leukemia subsequent to a myelodysplastic/myeloproliferative disorder. Hence, the distribution of poor-risk categories was essentially the same as that in the present series. Remission was achieved in 42% of the 67 patients, while 34% expired during therapy. When these data are considered together with the data described above, it is clear that the alteration of the 12-dose regimen to the modified regimen described here was associated with a lower remission rate and a comparable mortality rate. The incidence of specific toxicities was also similar for the 12-dose and 8-dose regimens. For example, each was associated with CNS toxicity (14% vs 21%), infection (82% and 61%), and hemorrhage (41% vs 35%), where the first value in each parenthesis represents the incidence for the 12-dose regimen and the second value the incidence among patients treated with the modified regimen.

A major reason for the failure of the modified regimen to improve the treatment outcome was the lesser antileukemic efficacy of the 8 dose course of therapy. This had been noted in a smaller number of patients treated during the initial phase I studies [4] and was demonstrated in the present study in two ways. Of 27 patients, 20 (74%) failed to enter remission after the 8-dose course of therapy because of inadequate antileukemic effects (see Table 1),

whereas only 29% of patients treated with 12 doses of cytosine arabinoside failed to enter remission because of persistent leukemia. Consistent with the lesser antileukemic efficacy of eight doses of drug are the data regarding the reduction in marrow leukemic cell mass. Eight doses of drug produced only two-thirds the reduction produced by 12 doses (70% vs 99%, respectively). We do not believe that the use of a dose of 2 g/m^2 instead of 3 g/m^2 was responsible for the reduced therapeutic efficacy, since the lowering of the dose to 2 g/m^2 when the 12-dose regimen was used resulted in an increase in the complete remission rate in patients over 70 years of age from 17% to 53% [10].

Other investigators have attempted to reduce the toxicity of high-dose cytosine arabinoside by reducing the dosage to 0.5 g/m^2 and administering the drug together with doxorubicin and vincristine [12]. This drug combination has produced a high remission rate in a fairly young standard-risk patient population with relapsed disease. Whether these data are applicable to the high-risk patient population reported here is unknown at the present time.

In data soon to be published we have demonstrated that the in vivo intracellular araCTP levels in leukemic cells following the administration of 2 g/m^2 are indistinguishable from those achieved when 3 g/m^2 is administered (Y. Rustum 1986, to be published). Hence, it appears that it is not necessary to administer cytosine arabinoside at 3 g/m^2. We are presently performing studies of 12-dose courses at dose levels of 2, 1.5, and 1.0 g/m^2 together with the selective administration of daunorubicin to patients whose day-6 marrow contains substantial numbers of residual leukemic cells. In this way we hope to define the lower limit of high-dose cytosine arabinoside therapy and to improve the remission rate by selective tailoring of the intensity of the regimen to the characteristics of the individual patient.

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