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High-dose cytosine arabinoside: response to therapy in acute leukaemia and non-Hodgkin's lymphoma*

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Summary. *Twenty-six patients with acute leukaemia and 14 with high-grade lymphoma received cytosine arabinoside (ara-C) at a twice daily dose of 2 g/m² administered as a 3-h infusion. Thirty-four patients received 12 doses and six electively received four doses only. Complete remission was achieved in six of seven patients with acute myelogenous leukaemia (AML), one of two evaluable patients with blast crisis of chronic myeloid leukaemia and three of eight patients with acute lymphoblastic leukaemia (ALL). Three further patients with ALL had only minimal bone marrow infiltration after one cycle, toxicity precluding administration of a second. Three patients with AML who received four doses only showed no evidence of response. Four of 14 patients with lymphoma who received 12 doses, entered complete remission. Five additional patients died with minimal residual disease whilst severely neutropenic. A complete and a partial response were seen in two patients with immunoblastic and centrocytic lymphoma respectively who received four doses. These results confirm the activity of high-dose ara-C in patients with AML and suggest that it may also be a potentially useful agent in ALL and high-grade lymphoma, especially as the incidence of CNS toxicity is lower than that reported at higher doses.*

Introduction

Cytosine arabinoside (ara-C) is a well-established remission induction agent in acute myelogenous leukaemia (AML). Until comparatively recently continuous intravenous infusion was generally held to be the most effective schedule, reflecting the apparent complete S-phase specificity of the drug [7]. During the past 3 years, however, it has been demonstrated that it is possible to administer much higher doses by short intravenous infusion and induce remission of AML in selected patients shown to be refractory to ara-C given continuously at conventional doses [1–6, 8, 13].

The most widely used "high-dose ara-C" schedule to date has been 3 g/m², infused over 1 or 3 h, every 12 h, to a maximum of 12 doses, with or without asparaginase "rescue" [1–5]. This was derived from the phase I experience of Rudnick et al. [8], and is associated with side-effects which are different from those seen with lower doses given by continuous infusion. Cerebellar toxicity, particularly in patients who have received prior intrathecal therapy or cranial irradiation, conjunctivitis and exfoliative dermatitis have been reported. Prolonged myelosuppression also occurs, though gastro-intestinal symptoms are less frequent.

A phase II study of ara-C at a dose of 2 g/m², given 12 hourly, was therefore undertaken in patients with acute leukaemia and non-Hodgkin's lymphoma (NHL) who had failed to enter remission or had relapsed following conventional therapy. The objective of the study was to determine whether this dose could result in equivalent anti-leukaemic activity with less central nervous system (CNS) toxicity than that encountered at 3 g/m². The feasibility of administering high-dose ara-C as consolidation therapy to patients in remission of AML was also evaluated. The results achieved with one cycle of therapy are presented.

Patients and methods

Patients. Forty-six adults (age range 20–68 years, mean 39, median 37) and three children (aged 8, 12 and 15 years) received a total of 52 cycles of treatment. Forty patients received 12 doses (Table 1); 32 had either failed to enter remission or had relapsed following conventional therapy, whilst five, with blast crisis of chronic myeloid leukaemia (CML Bc) had received no prior therapy. Three patients with AML, in whom first remission had been achieved with adriamycin, ara-C and 6-thioguanine, received high-dose ara-C alone as consolidation therapy. Six patients electively received four doses only (Table 2).

Table 1. Clinical details: patients receiving 12 doses

Acute leukaemia		Non-Hodgkin's Lymphoma	
Diagnosis	No. of patients	Diagnosis	No. of patients
AML	7	Immunoblastic	5
AML (in CR)	3	Lymphoblastic	2
ALL	8	Centroblastic	1
AUL	2	Burkitt	1
T-cell lymphoma/ leukaemia (HTLV)	1	Centrocytic	5
CML B.Cr.	5		
Total	26	Total	14

AML, acute myelogenous leukaemia; CR, complete remission; ALL, acute lymphoblastic leukaemia; AUL, acute undifferentiated leukaemia; CML B. Cr., blast crisis of chronic myeloid leukaemia

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Table 2. Clinical details: patients receiving 4 doses

Diagnosis	No. of patients
AML	3
AUL	1
Centrocytic lymphoma	1
Immunoblastic lymphoma	1
Total	6

Table 3. Response in patients with leukaemia receiving 12 doses

Diagnosis	No.	CR	Evidence of response	Resistant disease	Early Death
AML	7	6	0	1	0
ALL	8	3	3	1	1
AUL	2	0	1	1	0
HTLV	1	0	0	0	1
CGL B. Cr.	5	1	0	1	3
Total	23	10	4	4	5

Schedule. Ara-C was infused over 3 h every 12 h, at a dose of 2 g/m^2, a total of 12 doses in 6 days being given in each cycle. A second cycle was administered to four patients (1 ALL, 1 AML, 2 NHL), two of whom (1 AML, 1 NHL) received a third cycle. One patient was treated with ara-C in combination with adriamycin 30 mg/m^2 on day 1. All patients received prophylactic oral non-absorbable antibiotics [9] and prednisolone eye drops were prescribed 2 hourly for 10 days.

Results

Response to therapy

Leukaemia: 12 doses (Table 3). The degree of bone marrow infiltration decreased from 50% to 90% blasts in a hypercellular marrow to minimal or no leukaemia in 14 of 18 patients evaluable for response. Complete remission was acieved in six of seven patients with AML and in three of the eight patients with acute lymphoblastic leukaemia (ALL). Three more patients with ALL had only minimal leukaemic infiltration after one cycle (toxicity precluding administration of a second) and one patient died of cerebral haemorrhage in aplasia. Complete remission was also achieved in one patient with lymphoid blast crisis of CML.

A very short-lived response was seen in a patient with acute undifferentiated leukaemia (AUL) in whom rapid disappearance of all demonstrable disease (lymphadenopathy and skin infiltration) was associated with only minimal residual bone marrow infiltration. However, 4 weeks after the completion of ara-C, relapse occurred at the same extramedullary sites.

A patient with T-cell leukaemia/lymphoma (HTLV) died of fungal pneumonia with minimal leukaemic infiltration. Four patients (1 AML, 1 ALL, 1 AUL and 1 CML-Bc) showed no evidence of response and three of four patients with CML-Bc (all myeloid) died before being evaluable for response.

Patients with lymphoma: 12 doses (Table 4). Nine of 14 patients responded rapidly to one cycle of treatment. Complete remission was achieved in four patients (1 T-cell lymphoblastic, 2 immunoblastic, 1 centrocytic) and resolution of hepatosplenomegaly and lymphadenopathy was seen in a further five patients (1 immunoblastic, 1 centroblastic, 3 centrocytic) who died with minimal or no residual disease whilst severely neutropenic. Four patients (1 lymphoblastic, 1 immunoblastic, 1 centrocytic and 1 Burkitt) did not respond.

Table 4. Response in patients with lymphoma receiving 12 doses

Diagnosis	No.	CR	Resistant disease	Early death
Immunoblastic	5	2	2	1
Lymphoblastic	2	1	1	0
Centroblastic	1	0	0	1
Burkitt	1	0	1	0
Centrocytic	5	1	1	3
Total	14	4	5	5

4 doses. In two of three patients with AML, blasts cleared temporarily from the peripheral blood, but there was no change in the degree of bone marrow infiltration. The third patient showed no evidence of response. One patient with AUL was inevaluable for response due to early death. Complete remission was achieved after two cycles (administered at an interval of 28 days) in a patient with immunoblastic lymphoma and a partial remission was observed after one cycle in a patient with centrocytic lymphoma.

Duration of response. Response were short-lived: relapse occurred in four patients with AML within 9 months and in two patients with ALL at 2 and 10 months, respectively. Patients with lymphoma also relapsed early, three patients who received 12 doses relapsing within 5 months and progressive disease becoming manifest within 3 months in the two patients who received four doses only.

Clinical toxicity

Alopecia was universal and all patients complained of nausea and vomiting particularly on the first 2 days of therapy. Seven patients developed severe conjunctivities despite prednisolone eye drops. Fever was ascribed to the ara-C infusion in one patient. Two patients developed exfoliative dermatitis and one patient with localised lymphoma, who had previously received radiotherapy, had a skin reaction in the irradiated field. There was no cumulative toxicity in three of four patients receiving more than one cycle. However, one patient with immunoblastic lymphoma, who had relapsed early following six cycles of intensive combination chemotherapy, died of bronchopneumonia with no demonstrable disease whilst profoundly neutropenic following a second cycle.

One of the nine patients who had previously received both intrathecal chemotherapy and cranial irradiation developed cerebellar signs on day 10, but recovered completely within 5 days on oral dexamethasone. However, none of the seven patients who had received only intrathecal chemotherapy developed signs of cerebellar dysfunction. A patient with NHL, who had received neither, became confused and disorientated and subsequently had a grand mal seizure 6 h prior to death from septicaemia. No autopsy was performed, so it is impossible to attribute this with certainty to ara-C.

Table 5. Duration of neutropenia

Diagnosis	Neutrophil count	
	$0-0.1 \times 10^9$/l	$0.1-1.0 \times 10^9$/l
	Mean no. of days (range)	Mean no. of days (range)
Leukaemia (remission induction)	14 (10–20)	4 (0–6)
AML (consolidation)	13 (10–21)	4 (0–7)
Lymphoma	14 (11–20)	5 (0–7)

Administration of ara-C as consolidation therapy to three patients with AML was not associated with toxicity other than nausea and vomiting and myelosuppression (vide infra). These patients had previously received at least two cycles of adriamycin 75 mg/m^2 over 2 days, ara-C 200 mg/m^2 per day by continuous intravenous infusion and 6-thioguanine 200 mg/m^2 per day, both for 7 days.

Myelosuppression (Table 5)

Myelosuppression was prolonged and profound in patients receiving 12 doses. The duration of neutropenia was the same for patients with leukaemia and lymphoma. The duration of neutropenia in patients receiving ara-C as consolidation therapy was the same as in a previous cycle of consolidation therapy comprising adriamycin, ara-C and 6-thioguanine (neutrophils less than 0.1×10^9/l for 15, 14, and 11 days).

One patient with AML received one cycle of ara-C as remission induction therapy, one cycle as consolidation, followed by a third cycle in combination with adriamycin 30 mg/m^2 on day 1. The neutrophil count was less than 0.1×10^9/l for 19, 15, and 20 days respectively.

A total of 13 patients (2 with resistant disease) died whilst severely cytopenic, 10 of infection and three of cerebral haemorrhage. Six of 35 patients aged under 50 years of age died during therapy compared with seven of 14 patients aged over 50.

Discussion

These results concur with those in the literature in the demonstration that ara-C administered at high dose by short intravenous infusion twice daily results in rapid lysis of AML, regardless of whether the patients have previously received the drug in conventional dose and schedule. It has also been confirmed that treatment needs to be continued for more than 2 days to be effective.

In addition, high-dose ara-C has been shown to be highly active in both lymphoblastic leukaemia and high-grade lymphoma. The discrepancy between the very high response rate but relatively low complete remission rate is at least in part a function of therapy being changed after one cycle, not because of failure to respond, but because of toxicity. This was severe and life-threatening with prolonged and profound neutropenia. The mortality in patients with lymphoma, all of whom had previously received numerous cycles of intensive chemotherapy, was appreciable, perhaps reflecting the fact that these patients were older. The degree of myelosuppression was, however no worse than that observed with conventional remission induction therapy for AML [10].

Neurotoxicity occurred less frequently than in series utilising 3 g/m^2 [4, 5] in spite of seven patients having received prior intrathecal chemotherapy and a further nine both intrathecal therapy and cranial irradiation. It has been demonstrated that when 2 g/m^2 of ara-C is administered over 1 or 3 h, CSF ara-C concentrations are the same, irrespective of the duration of the infusion [11]. However, there is a linear relationship with dose. Therefore, the low incidence of cerebellar toxicity in this study compared with others probably reflects the lower dose rather than the modification in schedule. The remainder of the toxicity was acceptable, with gastro-intestinal disturbance being considerably less severe and less frequent than when ara-C is given by continuous intravenous infusion. Conjunctivities and dermatitis, whilst occasionally severe, responded to local or systemic corticosteroids.

It remains to be determined whether the apparent enhancement in the activity of ara-C resulting from the administration of higher doses is of practical relevance to patients with acute leukaemia and high-grade malignant lymphoma. Little information is available about the long-term benefits of such therapy, though in this study the time to recurrence was usually short. This is not surprising, in view of the fact that all the patients had failed what was considered to be optimal therapy. It seems justifiable, however, to consider the introduction of one or two cycles of high-dose ara-C as part of the initial treatment of these diseases, particularly in selected groups of patients for whom the prognosis is expected to be poor. The potential advantage of this approach in lymphoid malignancy lies in the high prolonged concentrations of the drug achieved in the cerebrospinal fluid, possibly providing, in addition to the systemic effect, protection against CNS infiltration.

Any enthusiasm generated by these exciting results should, however, be tempered by the knowledge that the early promise of high-dose methotrexate has sadly not been widely fulfilled. Should the further investigation of high-dose ara-C continue to be fruitful, it may be appropriate to consider it being tested in randomised clinical trials.

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