Cancer Chemother Pharmacol (1987) 19: 169–171

Cancer Chemotherapy and Pharmacology

A phase II study of high-dose cytosine arabinoside in the treatment of acute leukaemia in adults

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Summary. Twenty-seven adults with refractory or recurrent acute leukaemia were treated with cytosine arabinoside (ara-C) 2 g/m^2 infused over 3 h, every 12 h for 6 days, either alone (regimen A) or with vincristine and prednisolone (regimen B). Complete remission was achieved in 9/18 patients (5/12 regimen A, 4/6 regimen B) with acute lymphoblastic leukaemia (ALL), 1/7 patients (1/5 regimen A) with lymphoid blast crisis of chronic myeloid leukaemia (CML.LBC) and 1/2 patients (1/1 regimen B) with acute undifferentiated leukaemia (AUL). A further 5 patients (4 regimen A, 1 regimen B) with ALL, 4 patients (3 regimen A, 1 regimen B) with CML.LBC and 1 patient (regimen A) with AUL showed evidence of significant response. These results confirm the activity of high-dose ara-C in acute non-myelogenous leukaemia and suggest that it might be used with benefit to intensify the initial treatment of 'poor-risk' ALL.

Introduction

Acute lymphoblastic leukaemia (ALL) is ultimately fatal for most adults with the disease, despite the fact that complete remission (CR) may be achieved in the majority [2, 3]. Recurrence in the bone marrow is the main problem, and is assumed to reflect failure of the initial therapy to eradicate the process. Attention therefore has been focused on methods of improving the early therapy, thereby hopefully preventing relapse [8, 13].

Cytosine arabinoside (ara-C) has proven efficacy in ALL [9, 16] and crosses the blood-brain barrier in significant concentrations [7]. In 1979, Rudnick et al. reported on the effectiveness of high-dose ara-C (1.0–7.5 g/m^2) in the treatment of acute leukaemia refractory to the drug in conventional dosage [12]. The attractiveness of this approach, with particular regard to ALL, was furthered by the demonstration that, following high-dose systemic therapy, prolonged levels of the drug could be achieved in the cerebrospinal fluid (CSF), which might be expected to be antileukaemic [15].

A phase II study of high-dose ara-C in acute non-myelogenous leukaemia was therefore undertaken to determine whether it might subsequently be used to intensify the initial therapy of ALL. A dose of 2 g/m^2 (rather than the more commonly used 3 g/m^2) was employed in an attempt to avoid central nervous system (CNS) toxicity [11].

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Materials and methods

Patients (Table 1). Twenty-seven patients with acute leukaemia (18 ALL, 7 CML.LBC and 2 AUL) were entered into an open study between July, 1981 and April, 1985. At the outset, patients received high dose ara-C alone. In the latter part of the study, all received vincristine and prednisolone as well unless they had previously been shown to be resistant to it. Ten of the patients with ALL were treated at first relapse, two at second relapse and one at third relapse. The other five patients were treated when refractory to conventional therapy (2 at presentation, 2 at first relapse and 1 at second relapse). All of the patients with acute lymphoblastic leukaemia and acute undifferentiated leukaemia had previously received vincristine and prednisolone. Nineteen had received adriamycin and l-aspar-

Table 1. Patients' details

	ALL ($n = 18$)	CML.LBC ($n = 7$)	AUL ($n = 2$)
Age (years)			
Range	18–66	19–65	21, 53
Median	28	47	
Sex M:F	13:5	3:4	1:1
Blast cell count (x10^9/l)			
Range	0–164	0.5–104	2.0, 2.8
Median	0.7	20.4	
Morphology L1:L2 (FAB)	1:17		
Immunophenotype			
Common ALL	6		
Null ALL	4		
T-cell ALL	6		
Untested	2		
Previous CNS treatment			
IT	2	0	0
IT+RT	15	0	2

ALL, acute lymphoblastic leukaemia; CML.LBC, lymphoid blast crisis of chronic myeloid leukaemia; AUL, acute undifferentiated leukaemia, morphologically
IT, intrathecal chemotherapy alone; IT+RT, intrathecal chemotherapy and cranial irradiation

Table 2. Details of treatment regimens

Drug	Dose	Days
Regimen A		
Cytosine arabinoside (i.v.)	2 g/m² b.d.	1–6
Regimen B		
Cytosine arabinoside (i.v.)	2 g/m² b.d.	1–6
Vincristine (i.v.)	2 mg	1
Prednisolone (p.o.)	40 mg	1–6

Ara-C was infused over 3 h every 12 h for 12 doses

aginase in addition. Fifteen had received cyclophosphamide. Five of the patients with CML.LBC were treated having progressed from the chronic phase and two having presented de novo in blast crisis. One of the patients with AUL was treated at first relapse and the other when refractory at second relapse. Two of the patients with chronic myeloid leukaemia had received no previous therapy. Four had received busulphan (2 of these had received interferon as well) and one had received hydroxyurea.

Treatment regimens (Table 2). Eighteen patients were treated with regimen A and nine with regimen B. Prednisolone eye drops were prescribed every 2 h for 10 days from the commencement of ara-C.

Supportive care. All patients were nursed in an open ward and received prophylactic non-absorbable antibiotics. Platelet transfusions from single donors were given prophylactically to maintain the platelet count over 20×10^9/l, or if clinically indicated. Fever was assumed to be due to bacterial infection and treated with broad-spectrum antibiotics.

Results

Response to treatment (Table 3)

ALL. Complete remission was achieved in 9/18 (5/12 patients treated with regimen A and 4/6 with regimen B). In addition, there was reduction of bone marrow infiltration to less than 10% blasts in a further 5 patients, in 4 of whom the peripheral blood returned to normal (4 treated with regimen A and 1 with regimen B). Two of the patients in whom CR was achieved with regimen A had been refractory to vincristine, prednisolone, adriamycin and l-asparaginase (1 at presentation and 1 at first relapse).

In 2 patients with ALL the CSF was involved at bone marrow relapse, and in a third patient both the CSF and bone marrow had been involved and refractory to treatment at presentation. The first 2 patients received a single intrathecal injection of methotrexate prior to high-dose ara-C, and the CSF thereafter was clear. In the third patient the disease was refractory to high-dose ara-C in both the bone marrow and the CSF.

CML.LBC. Complete remission was achieved in 1/5 patients treated with regimen A. In addition, 2 patients reverted to chronic phase and in 1 patient, who died of infection whilst neutropenic, there was reduction of bone marrow infiltration to less than 5% blasts. In 1 patient treated with regimen B bone marrow infiltration was reduced to less than 10% blasts, but the peripheral blood count never returned to normal.

AUL. Complete remission was achieved in 1 patient treated with regimen B. In the second patient, bone marrow infiltration was reduced to less than 5% blasts with regimen A, the blood count returning to normal.

Duration of response

All the patients in whom CR was achieved received further chemotherapy as consolidation. Of the 9 patients with ALL, 5 were treated with between two and four cycles of vincristine, prednisolone and adriamycin (OPA), 2 with further high-dose ara-C and 2 with intensive chemo-radiotherapy supported by autologous bone marrow transplantation. The patient with CML.LBC in whom CR was achieved was treated with five cycles of OPA, and 1 of the 2 patients who reverted to chronic phase received further high-dose ara-C. The patient with AUL in whom CR was achieved was treated with three cycles of OPA.

Excluding the 2 who proceeded to chemo-radiotherapy, bone marrow relapse occurred within 2–12 months (median 7) in all the patients with ALL but 1, who remains in remission at 8 months. A combined bone marrow and CSF relapse occurred in the patient with CML.LBC at 5 months and a bone marrow relapse in the patient with AUL at 3 months.

The chronic phase was maintained in the 2 patients with CML for 6 and 5 months respectively before reversion to CML.LBC occurred, associated with CSF involvement in 1.

Toxicity (Table 4)

All patients developed alopecia and most experienced nausea and vomiting. The majority of patients developed diarrhoea, which in two was associated with ileus and in one with a presumed perforated abdominal viscus, all of which settled with conservative management. Twelve patients complained of sore eyes despite steroid eye drops,

Table 3. Response to treatment

	Regimen A ($n = 18$)			Regimen B ($n = 9$)		
	CR	Response	Fail	CR	Response	Fail
ALL ($n = 18$)	5	4	3	4	1	1
CML.LBC ($n = 7$)	1	3	1	0	1	1
AUL ($n = 2$)	0	1	0	1	0	0

Table 4. Toxicity of regimens A and B

	Regimen A ($n = 18$)	Regimen B ($n = 9$)
Nausea and vomiting	14	7
Diarrhoea	12	8
Ileus	1	1
Ocular discomfort	7	5
Blistering skin reaction	1	1
Macular rash	4	3
Cerebellar syndrome	1	0

Table 5. Duration of neutropenia

Neutrophil count ($x10^9/l$)	Mean no. of days (range)		
	0–0.1	0.1–0.5	0.5–1.0
Regimen A ($n = 15$)	15 (9–21)	3 (2–8)	2 (1–6)
Regimen B ($n = 9$)	13 (10–16)	3 (1–6)	2 (1–3)

and in three this was severe, although no permanent sequelae occurred. Two patients developed a severe, extremely painful skin reaction predominantly involving the palms of the hands and soles of the feet, which later blistered and desquamated.

One patient, a 37-year-woman who had previously received intrathecal chemotherapy and cranial irradiation, developed dysarthria and ataxia on day 7, but recovered completey within 10 days. Another patient developed slurring of speech after 7 doses of ara-C whilst also receiving anti-emetic medication. It resolved after 12 h, and the remaining doses were given at 1 g/m^2 without further complications.

The duration of neutropenia in those patients whose blood counts recovered is shown in Table 5. The three patients whose blood counts did not recover had all failed to respond to treatment.

Discussion

This study confirms the efficacy of high-dose ara-C in acute non-myelogenous leukaemia, and that the schedule of administration is feasible. Furthermore, the results are comparable to those reported by others for ALL [4] and CML.LBC [5] using schedules employing a 3 g/m^2 dose of ara-C.

The toxicity was severe, as expected, but in the main manageable. Myelosuppression was prolonged, but was no worse than that observed with conventional induction therapy for AML [14]; and gastro-intestinal toxicity, in general, was less than that encountered with continuous-infusion ara-C [14]. The severe corneal toxicity produced by high-dose ara-C was for the most part preventable by steroid eye drops [10]. The incidence of CNS toxicity was low, even though over half the patients had previously received both intrathecal chemotherapy and cranial irradiation. On review, advanced age, and not prior CNS treatment, appears to be the major risk factor for the development of cerebellar syndrome [1, 6].

In conclusion, these results are encouraging and suggest that high-dose ara-C might be used with benefit to intensify the initial treatment of 'poor-risk' ALL.

Acknowledgements. We are pleased to acknowledge the contribution of the medical and nursing staff of Annie Zunz and Dalziel Wards, St Bartholomew's Hospital. The immunophenotype was determined by Professor M. F. Greaves (Leukaemia Research Fund Centre, Institute of Cancer Research) until October, 1984, and thereafter by Dr. M. A. Horton (Haemopoiesis Laboratory, St Bartholomew's Hospital). We are grateful to the Upjohn Company for providing the cytosine arabinoside. Finally, we thank Jane Ashby for typing the manuscript.

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Received April 14, 1986/Accepted August 21, 1986