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The Feasibility of Opal/High Dose Ara-C Treatment of Adult Acute Lymphoblastic Leukaemia *

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A. Introduction

Studies conducted at St. Bartholomew's Hospital between 1972 and 1982 into the treatment of acute lymphoblastic leukaemia (ALL) in adults showed a complete remission (CR) rate of 65% (73/112) using a combination of vincristine, prednisolone, adriamycin, and L-asparaginase, with CR frequency being highest in young patients and lowest in those with L3 morphology. The duration of remission correlated closely with blast cell count at presentation and the surface phenotype of the blast cells, being significantly longest in patients with low blast counts of common ALL antigen (CALLA) positivity. Central nervous system (CNS) relapse alone was relatively frequent in those patients in whom the cerebrospinal fluid (CSF) was positive at the first lumbar puncture (3/13) despite craniospinal or cranial irradiation and intrathecal therapy. However, by far the greatest problem was bone marrow relapse alone, or in association with relapse at other sites, e.g. CSF, testis, skin (43/53) and was not reduced by introducing escalating doses of adriamycin and cyclophosphamide into the early therapy [1].

Recent experience with the use of high dose cytosine arabinoside (Ara-C) in the treatment of both ALL in relapse and the lymphoid blast crisis of chronic myeloid leukaemia has been encouraging with a response being achieved in 9/14 patients after one cycle (Barnett MJ, unpublished observations), and supporting our initial results [2]. In addition, pharmacokinetic studies of the concentration of Ara-C in the plasma and CSF have shown that, when given intravenously in high doses, prolonged levels of the drug can be achieved in the CSF, which should be effective in the treatment of CNS leukaemia [3].

In December, 1982 an open study commenced with the intention of exploiting the systemic and CSF activity of high dose Ara-C in the initial therapy of adults with ALL at St. Bartholomew's Hospital. Preliminary results to demonstrate the feasibility of the programme are presented below.

B. Patients and Methods

A total of 13 previously untreated patients have so far been entered into the study (Table 1), using the treatment regimen shown in Fig. 1. Ara-C was infused over 3 h every 12 h at a dose of 2 g/m^2, a total of 12 doses being given over 6 days. All patients received prophylactic nonabsorbable antibiotics and prednisolone eyedrops were prescribed every 2 h for 10 days from the commencement of the Ara-C. Maintenance therapy comprises oral 6-mercaptopurine (daily), cyclophosphamide and methotrexate (weekly) for 3 years. During this time intrathecal injections of methotrexate or Ara-C are given every 2 months.

C. Results

All 13 patients received the treatment programme as planned at least to the com-

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pletion of the Ara-C. The Ara-C was stopped after 11 doses in one patient, and after 10 doses in two patients owing to the development of severe skin reactions in two and nystagmus in the third. There was no evidence of leukaemia in 8/13 patients prior to administration of Ara-C. Seven patients entered CR, the eighth dying of pseudomembranous colitis without peripheral blood recovery on day 19 following Ara-C administration. Five patients had residual leukaemia prior to Ara-C administration, of the three evaluable for response, two had obvious residual leukaemia following Ara-C treatment, and in the third, in whom the bone marrow was heavily infiltrated before Ara-C treatment, there was no detectable leukaemia afterwards, but persistent cyto-

Table 1. Patients ($N = 13$)

Sex	M:F	8:5
Age (years)	Range	18–55
	Mean	36
	Median	34
Blast count ($\times 10^9$/l)	Range	0–279
	Mean	34
	Median	2.1
Morphology	L1	3
	L2	10
	L3	0
Phenotype	C-ALL	2
	N-ALL	5
	T-ALL	2
	B-ALL	1
	Uncertain	2
	Untested	1
CSF	Positive	0
	Negative	12
	Untested	1

Table 2. Toxicity and myelosuppression

Ara-C Toxicity		No. of patients
Nausea and vomiting		11
Skin	Blistering reaction (palms and soles)	7
	Macular rash	4
Diarrhoea		8
Ocular discomfort		4
Neurological	Tremor	2
	Nystagmus	1
	Grand mal fits (see text)	1

Duration of myelosuppression neutrophils ($\times 10^9$/l)

		0–0.1	0.1–0.5	0.5–1.0
Time (days)	Mean	12	2	2
	Range	(7–19)	(0–5)	(1–3)

NB: These data relate to 9 patients and exclude one (see text) in whom the duration of myelosuppression was

	0–0.1	0.1–0.5	0.5–1.0
Time (days)	13	22	34

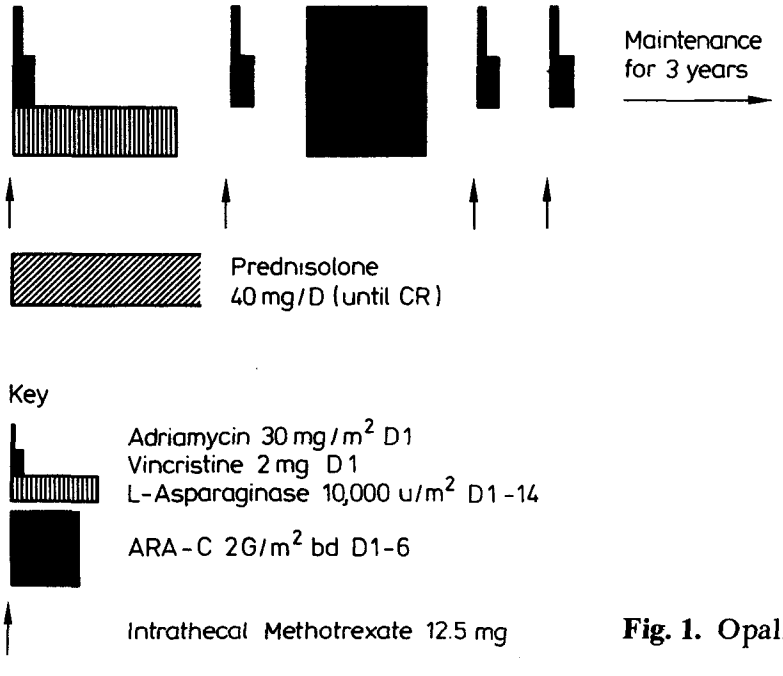

Fig. 1. Opal/high dose Ara-C regimen

penia, and recovery of the peripheral blood coincided with recurrent leukaemia. Two patients died before peripheral blood recovery, one on day 14 with *Pseudomonas* septicaemia and the other, who died on day 13, had bronchopneumonia and bone marrow infiltration at post-mortem examination. Of the seven patients entering CR, six remain in remission, one having had bone marrow relapse.

Toxicity related to the Ara-C is shown in Table 2. One patient, a 22-year-old female, developed grand mal epileptic fits on day 19 following Ara-C treatment and a CT head scan showed patchy areas of low attenuation in the occipital and parietal lobes. A repeat scan 5 weeks later was normal and she recovered completely with no sequelae.

D. Discussion

The major problem in the treatment of ALL with conventional therapy is bone marrow relapse. High dose Ara-C has been used to intensify the initial systemic therapy, as well as providing CNS prophylaxis and thus obviating the need for cranial irradiation. In the limited number of patients entered into the study so far, the CR rate was 55% (7/13) compared with 65% (73/112) in the previous study. The low CR rate is disappointing, particularly as at least three of the five patients who had leukaemia prior to the Ara-C treatment had persistent leukaemia afterwards, and none entered CR. However, the patient population in this study has a median age 8 years older than the previous one, and also an unusual membrane phenotype distribution.

Although the toxicity from high dose Ara-C was considerable, except for the high incidence of severe skin reactions which was unexpected, it was predictable from our previous experience. It is certainly feasible to administer high dose Ara-C in close proximity to the conventional combination chemotherapy. Whether or not the toxicity is acceptable will be determined by the effect of the regimen on long-term survival.

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