Oral methotrexate is as effective as intramuscular in maintenance therapy of acute lymphoblastic leukaemia

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SUMMARY   It has been postulated that variations in methotrexate absorption may influence the outcome of treatment in lymphoblastic leukaemia. One hundred and forty four children with acute lymphoblastic leukaemia not of the T cell type were randomised to receive continuing treatment with daily 6-mercaptopurine, vincristine, and prednisolone six weekly and methotrexate once weekly, either as a single oral dose or an intramuscular injection. Analysis of results with a minimum follow up of three and a half years has shown that the route of administration of methotrexate has had no influence on relapse at any site, but more children receiving intramuscular methotrexate died in remission. These results indicate that oral methotrexate is as effective as intramuscular methotrexate in continuing treatment of lymphoblastic leukaemia.

Methotrexate is one of the two most widely used drugs in continuing (maintenance) treatment of acute lymphoblastic leukaemia. The drug is usually given by mouth but its absorption is variable[1][2] and influenced by factors such as timing and content of meals.[3] Parenteral administration of the drug circumvents the problem of variable absorption and thus might theoretically decrease the rate of bone marrow and testicular relapse in children with leukaemia by achieving more reliable blood concentrations. We report here the results of a clinical trial in which children with lymphoblastic leukaemia were randomly assigned to receive methotrexate weekly during continuing treatment, either by mouth or by intramuscular injection.

Patients and methods

All patients with acute lymphoblastic leukaemia not of T cell type, attending the Hospital for Sick Children between June 1979 and December 1982 were treated with the protocol as illustrated in Figure 1. Induction therapy consisted of oral prednisolone, subcutaneous L-asparaginase, and intravenous vincristine (Oncovin) and daunorubicin. Central nervous system (CNS) prophylaxis comprised intrathecal methotrexate on days 22 and 35 and four more doses at weekly intervals during and just after cranial irradiation. The dose was adjusted

for age as follows: up to 6 months, 3 mg; up to 1 year, 4 mg; up to 2 years, 5 mg; up to 4 years, 7.5 mg; and over 4 years, 10 mg. Cranial irradiation was given at a dose of 24 Gy in 15 fractions over three weeks until January 1981, when after the report from the children's cancer study group[4] the dose was reduced to 18 Gy in 10 fractions over two weeks. Radiotherapy was deferred in children under 2 years at the time of diagnosis; they received intrathecal methotrexate on three consecutive weeks after induction and then every six weeks until radiation, which was given soon after their second birthday.

After CNS prophylaxis patients received continuing treatment with methotrexate at a single weekly dose of 20 mg/m² given either first thing in the morning by mouth, before breakfast, or as a single intramuscular injection, 6-mercaptopurine for two weeks in three at an optimum dose of 75-100 mg/m², adjusted if necessary to maintain the neutrophil count above 1.0×10^9/l at the start of each two week course, and vincristine and prednisolone every six weeks. Patients were randomly assigned to receive their methotrexate either by mouth or as a single intramuscular injection. The protocol was designed so that patients received the standard dose of methotrexate throughout, with only 6-mercaptopurine being adjusted to the maximum tolerated dose. Prophylactic co-trimoxazole was
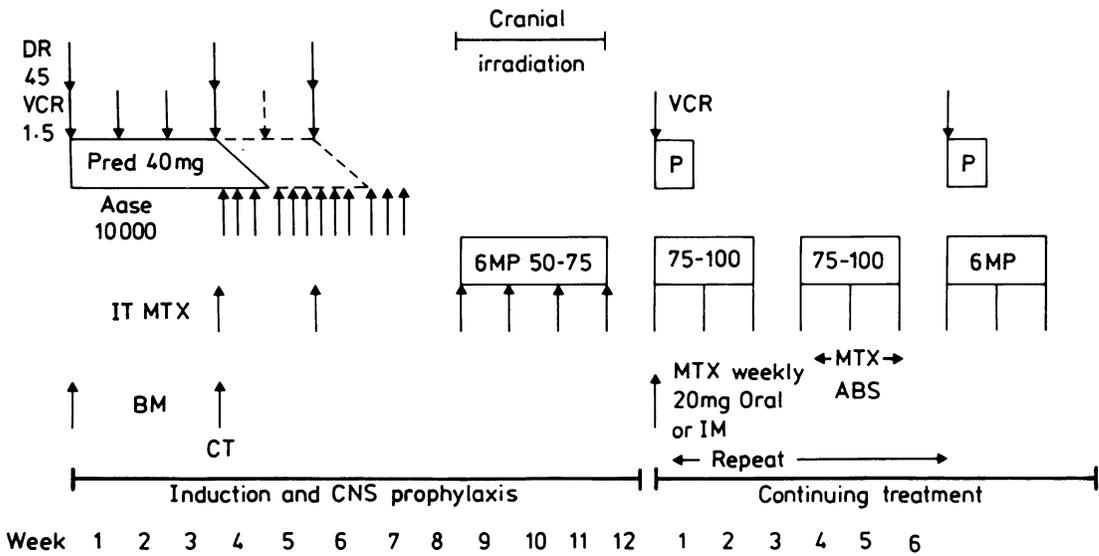
Fig. 1 *Design of the protocol. Numbers refer to doses of drug in mg/m²/surface area except for L-asparaginase, which is in units/m²/surface area.*

Pred, P=prednisolone; VCR=vincristine; Aase=L-asparaginase; DR=daunorubicin; 6MP=6-mercaptopurine; MTX=methotrexate; IT=intrathecal; IM=intramuscular; BM=bone marrow; CT=computed tomogram; CNS=central nervous system; ABS=absorption.

given only to patients who had had an episode of *Pneumocystis carinii* pneumonitis. This treatment was continued for 96 weeks of maintenance. Bone marrow examination, lumbar puncture, and, in boys, testicular biopsy examination were performed before stopping treatment.

Consent for randomisation was obtained verbally from the parents of all patients who were certain to be available for complete follow up. All other patients received oral methotrexate. Permission for the study was given by the joint committee on ethical practice of the hospital and institute.

All patients have been followed up for a minimum of three and a half years—that is, for at least 18 months after stopping chemotherapy—and median follow up of survivors who are free of disease is 62 months. Statistical analyses were performed by the log rank method.[5]

Results

Induction and randomisation. One hundred and sixty four patients were entered into the study, of whom 158 (96%) achieved remission, 154 at 21 days and the other four by 35 days. Two patients died during induction, one with renal failure and pulmonary haemorrhage and one, a boy with a history of bone marrow aplasia and jaundice, with septicaemia. Four patients were not in remission by 35 days, one boy with Ph' positive acute lymphoblastic leukaemia, one infant with leukaemia in association with a 4:11 translocation, and two boys with common acute lymphoblastic leukaemia and no obvious adverse prognostic factors.

One hundred and forty four of the patients were randomised to receive oral or intramuscular methotrexate. Table 1 gives details of the patients

Table 1 *Details of patients who were randomised**

Administration of methotrexate	(n=)	Sex (M:F)	Age (years)			Presenting leucocyte count (x 10⁹/l)		
			<2	2–10	>10	<20	20–50	>50
Oral	(75)	40:35	12	58	5	55	8	12
Intramuscular	(69)	34:35	6	57	6	49	15	5

*Fourteen patients were not randomised: seven with uncertain follow up studies, four who declined, two with radiotherapy violations, and one with CNS disease at presentation.

Table 2 First events in patients randomised

Administration of methotrexate	At risk		Any event			Death in remission	Relapse									Other‡
							Bone marrow*			Central nervous system*			Testis†			
	All	Boys	O	E	p Value		O	E	p Value	O	E	p Value	O	E	p Value	
Oral	75	40	27	30·18	} 0·19	1	18	18·12	} 0·48	6	5·8	} 0·48	5	6·07	} 0·26	1
Intramuscular	69	34	30	26·82		3	16	15·8		7	5·2		6	4·93		2

*Two combined central nervous system and marrow relapses in each group.
†Two combined marrow and testicular relapses on both oral and intramuscular methotrexate.
‡One relapse in each in ovary, eye, and lymph nodes.

who were randomised and also the reasons that 14 patients were not randomised. Of the two radiotherapy violations, one child developed arachnoiditis and was therefore given craniospinal irradiation rather than further intrathecal chemotherapy, and the second child developed an intracranial haemorrhage during induction and was therefore not given cranial irradiation.

Outcome in the patients who were randomised. The outcome in the two groups of patients is shown in Table 2 and Figure 2. There was no difference in the incidence of relapse at any site between patients receiving oral and intramuscular methotrexate, and disease free survival was similar in the two groups of patients. Actuarial disease free survival at 6 years, with 95% confidence limits, was 63·9 ($\pm$11)% for patients who received oral methotrexate and 51·2 ($\pm$15·8)% for those who received the drug intramuscularly. There were no differences revealed in relapse rate between the two groups either when patients were stratified by age, leucocyte count, or immunological subclass of leukaemia or when classified as average or poor risk on the basis of age and leucocyte count (Table 3).

The alteration in the dose of cranial irradiation was not made in a randomised way, but there is no significant difference yet in the CNS relapse rate between the two radiotherapy schedules, CNS
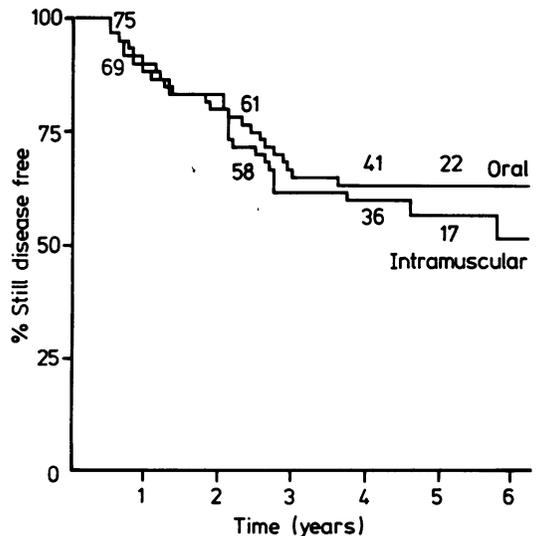

Fig. 2   Disease free survival from randomisation in children receiving oral and intramuscular methotrexate. The numbers on the graphs refer to numbers of patients at risk at the start of each 12 month period.

Table 3 *First event according to risk group*

	Administration of methotrexate				p Value (oral v intramuscular)
	Oral		Intramuscular		
	Events	No at risk	Events	No at risk	
Average	13	45	15	41	0·3
Poor	14	30	15	28	0·3

Average=Aged 2–10, initial leucocyte count <20×10⁹/l.
Poor=All other patients.

relapse occurring in six of 65 patients diagnosed before and seven of 79 diagnosed after 1981.

Toxicity. Induction therapy was well tolerated, with a mean time in hospital of eight days; 49 (30%) patients became febrile during induction and required a course of intravenous antibiotics for a presumed infection, which was serious in eight (5%). The infection rate during continuing treatment is shown in Table 4, where details are also given of the patients who were not randomised. Sixty children (38%) had at least one admission to hospital for presumed infection during treatment. The death rate during remission was 4%, half the deaths being due to measles. Two of the remission deaths occurred in children who had not been randomised, both with Down's syndrome and both probably due to mycoplasma pneumonia.

The major morbidity was due to fits, which occurred during or after treatment in two children randomised to oral and five randomised to intramuscular methotrexate. Computed tomogram changes suggestive of methotrexate radiation toxicity were seen in one child who suffered fits on oral methotrexate and in three of the five on intramuscular methotrexate.

Factors affecting duration of remission. As there was no significant difference in outcome between the

Table 4 *Infections during continuing treatment*

	Administration of methotrexate		
	Oral	Intra-muscular	All patients
Children admitted once or more during maintenance	29/75	28/69	60/158
Pneumocystis carinii	2 (1)	3	6 (1)
Varicella zoster	7	7	14
Measles	1	3 (3)	4 (3)
Mycoplasma pneumonia	2	1	5 (2)
Cytomegalovirus	1	0	1
Total deaths	(1)	(3)	(6) (4%)

*Deaths from infection in parenthesis.

Table 5 *Factors influencing disease free survival*

	p Value	Stratified for white blood cell count
Presenting leucocyte count	0·001	
Franco-American-British subtype	0·004	(0·01)
Age*	0·02	(0·05)
Phenotype*	0·021	(0·2)
Spleen size	0·07	(0·2)
Sex	NS	
Liver size	NS	
Lymph nodes	NS	
Haemoglobin	NS	

NS=Not significant.
*p=Value for heterogeneity.

two groups of patients, prognostic factors were assessed for all 164 children entering the protocol. The factors influencing prognosis are shown in Table 5, the most important being leucocyte count, age, and morphological subclass of acute lymphoblastic leukaemia.

Discussion

The protocol was in general well tolerated with a low morbidity. The addition of daunorubicin to prednisolone and vincristine during induction did not increase the incidence of serious infection in comparison with our previous series[6] and no adverse side effects were observed during the four week course of subcutaneous L-asparaginase. The choice of a semi-continuous regimen for continuing maintenance treatment was based on our own observations,[7] confirmed in the MRC UKALL V protocol,[8] that this type of schedule was as effective as the more conventional continuous regimen but less immunosuppressive. This is reflected in the fairly low incidence of serious infections during treatment. The continuing risk of measles remains, as we have previously reported, a cause for serious concern.[9]

Plasma methotrexate concentrations are extremely variable after oral administration and may be influenced by the timing and content of meals. While we attempted to standardise the time of methotrexate dose to achieve maximum plasma concentrations, we also suspected that giving the drug by injection might reduce the risk of bone marrow and testicular relapse. We were unable to show any benefit, however, for the intramuscular route, which was associated with a higher incidence of remission deaths, particularly in the low risk patients. The two deaths in patients on oral methotrexate who were not randomised occurred in patients with Down's syndrome, a group more at risk in view of their existing immunodeficiency.

Patients with T cell acute lymphoblastic leukaemia were not entered into the trial so that few patients had recognised adverse prognostic factors such as a leucocyte count in excess of $50 \times 10^9/l$. We have been unable, within the limitations of this small study, to determine any subgroup of patients for whom intramuscular methotrexate seemed to be superior.

These results are in apparent contradiction to those of the recently reported MRC UKALL VII trial,[10] a national study confined to standard risk patients (initial leucocyte count less than $20 \times 10^9/l$) that was conducted during the same period, but with many more randomised variables that could have affected the outcome, such as testicular irradiation, variable L-asparaginase during induction, and long term intrathecal methotrexate. Moreover, the methotrexate was given as a five day course every four weeks rather than weekly. In our trial, with similar numbers of standard risk patients, the route of administration of methotrexate was the only variable and proved to have no demonstrable effect on outcome. The factors influencing prognosis remained the traditional ones of age and leucocyte count. After stratification for these factors the morphological classification retained its prognostic importance, but patients with null cell leukaemia fared no worse than those with common cell leukaemia.

Further analyses of toxicity and pharmacokinetics are in progress, but it is of concern that a number of children developed convulsions during or after treatment and that four children developed computed tomogram changes suggestive of leucoencephalopathy, a complication described regularly only in children receiving intravenous methotrexate at a higher dose than our patients.

Thus, in summary, this trial suggests that intramuscular methotrexate is no better, and in fact is probably more harmful, than oral methotrexate in continuing (maintenance) treatment of childhood acute lymphoblastic leukaemia.

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