Intermediate Dose Methotrexate (IDM) in Childhood Acute Lymphocytic Leukemia (ALL)

Freeman, A. I.[1], Brecher, M. L.[2], Wang, J. J.[3], Sinks, L. F.[4]

1 Chief Department of Pediatrics, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, USA
2 Clinician II – Department of Pediatrics – Rosasell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, USA
3 Private Physician, 111 W. Beverly Boulevard, Montebello, California 90640, USA
4 Chief, Department of Pediatrics and Division of Adolescent Oncology, Vince Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C. 20007, USA

Abstract

We employed three courses of intermediate dose Methotrexate (IDM) added onto a standard induction and maintenance program with the concept of both central nervous system (CNS) prophylaxis and simultaneous systemic intensification. Cranial radiation (RT) was not employed as CNS prophylaxis.

Fifty of 52 patients (to age 18) achieved complete remission. Time on study now ranges from 22–68 months with a median time of 33 months. We separated the children into standard risk and increased risk. We defined increased risk as a WBC over 30000/mm^3 at presentation and an age of less than two years or greater than 10 years at presentation. There have been 15 relapses on these 50 patients; 11 occurred in increased risk patients (of 22 increased risk patients) and four occurred in standard risk patients (of 28 standard risk patients). There were seven CNS relapses, six systemic relapses, one simultaneous systemic and CNS relapse and one testicular relapse. Toxicity to the IDM was small with the worst problem being mucositis. No leukoencephalopathy occurred. The control of hematological relapse is excellent and the avoidance of potential long-term complications noted is even of greater importance.

Introduction

In the last 15 years there has been a remarkable improvement in the actual "cure" of children with acute lymphocytic leukemia (ALL) [1–7]. Primarily, this improvement has been due to the use of central nervous system (CNS) "prophylaxis" as well as effective systemic chemotherapy [1–7].

In the early 1960's, with the availability of effective Systemic therapy, but prior to effective CNS prophylaxis, it became apparent that approximately 50% of these children would develop CNS leukemia [8]. Once they

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developed CNS leukemia, very few were cured. In the mid 1960's, effective methods of CNS prophylaxis were first employed to prevent overt CNS leukemia and eventual systemic relapse and death. The technique of cranial RT and intrathecal methotrexate (IT MTX) as CNS prophylaxis reduced the incidence of CNS disease to approximately 10% [1–3,5,6]. In 1968, Cancer and Leukemia Group B (CALGB) in Protocol 6801, utilized prophylactic IT MTX and found that instead of 50% developing overt CNS leukemia, only 23% of the children developed this complication [4].

However, cranial RT clearly has limitations, i.e., it cannot eradicate leukemic cells in sanctuaries other than the cranial cavity, e.g., the gonads, etc. The long-term toxicity from prophylactic cranial RT also was a growing concern. Therefore in 1972, we began a study with the following objectives: a) to prevent the development of CNS leukemia without employing cranial RT, b) to intensify systemic therapy and thus eradicate leukemic cells in other sanctuaries and thereby improve the "cure" rate. We based this study on pharmacologic data which demonstrated that intravenous IDM at a dose of 500 mg/m^2 was capable of adequately entering the cerebrospinal fluid (CSF) [9], and hopefully simultaneously penetrate other sanctuaries to a like degree. This report describes the clinical results of this study.

Materials and Methods

52 patients with newly diagnosed ALL were treated according to the protocol depicted in Fig. 1 which was instituted in the Department of Pediatrics at Roswell Park Memorial Institute (RPMI) in August 1972. Following induction with steroid, Vincristine, and L-Asparaginase, three courses of IDM were administered at three weekly intervals. IDM was given at 500 mg per m^2 one-third by intravenous (IV) push and two-thirds by IV infusion over 24 hours. IT MTX at 12 mg/m^2 was given from one-half to two hours after the initiation of IV MTX. 24 hours following completion of IV MTX, a single dose of citrovorum factor (leucovorin) was given at 12 mg/m^2. With moderately severe mucosal ulceration, the subsequent course of IDM was delayed until there was complete healing. The next IDM was then given at full dosage, but an additional dose of leucovorin at 12 mg/m^2 was given 72 hours from the start of IDM (48 hours after completion of IDM). Following high dose MTX, the patient received maintenance therapy consisting of daily oral 6-mercaptopurine and weekly oral MTX and pulse doses of steroid and Vincristine (Fig. 1).

All children with ALL or acute undifferentiated leukemia who could not be identified as acute myelocytic leukemia or acute monomyelocytic leukemia were entered on the study.

From August 1972 until August 1976, when the study was closed to patient accrual, 52 patients were entered, ranging in age from 6 months to 17 years (Table 1). There were 26 females and 26 males at presentation.

Patients were classified as standard risk or increased risk in terms of age or WBC at presentation, i.e., those patients less than two years or greater

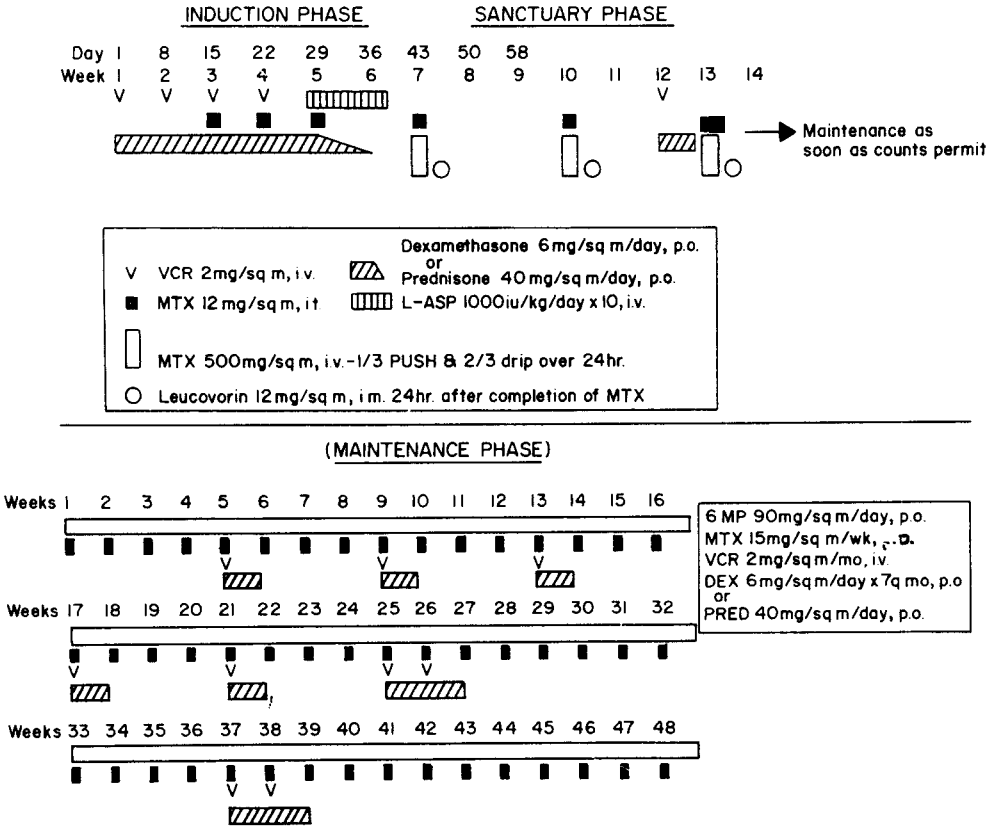

Fig. 1. Schema of treatment in ALL employing IDM

than 10 years of age and those patients who had a WBC greater than 30000 per mm^3 were defined as being increased risk (Table 1). In total, 24/52 children at diagnosis and 22/50 children who achieved complete remission were increased risk. Two children probably had CNS leukemia at diagnosis – one presented with papilledema and one had a right facial palsy of central type but when spinal taps were performed on these children two weeks later, no blasts were detected in the CSF.

Bone marrow aspirates were examined prior to the onset of therapy and

Table 1. Patient analysis at presentation

Number		52
Sex M:F		26:26
Achieved Complete Remission		50
CNS Leukemia at Diagnosis		2
Age	< 2 years	5
	> 10 years	11
WBC	> 100000/mm^3	5
	> 50000/mm^3	8
	> 30000/mm^3	12
Total Number with Increased Risk		22/50 (WBC > 30000/mm^3 or Age < 2 or > 10 years)

again at completion of the induction therapy and every 2–3 months thereafter, or at any time the peripheral blood was suspicious of a relapse. A remission bone marrow has normal granulopoiesis, thrombopoiesis, and erythropoiesis with fewer than 5% lymphoblasts and less than 40% lymphocytes plus lymphoblasts. Induction failure was defined as those patients not achieving a remission bone marrow (less than 5% blasts) by day 42.

For purposes of analysis, complete remission status was terminated by: 1. Bone marrow relapse (greater than 25% blast cells), 2. development of meningeal leukemia (>2 blast cells on cytologic preparations of the CNS or 10 cells/μl not attributable to chemical meningitis), 3. biopsy proven leukemic cell infiltration in extramedullary organs, and 4. death while in remission. Patients are taken off chemotherapy after four years of continuous sustained remission. There are now nine such patients.

All plots of remission duration were determined by actuarial life table analysis.

Results

The time on study now ranges from 22–68 months with a median time on study of 33 months.

Fifty of 52 patients (96%) achieved complete remission. The two induction failures were both in the increased risk group. To date, a total of 15 patients (30%) have relapsed (Table 2, Fig. 2). These included: 7 CNS relapses, 6 systemic relapses, 1 simultaneous systemic and CNS relapse, and 1 testicular relapse. Eleven of 22 increased risk patients (50%) and 4/28 standard risk patients (14%) have relapsed.

Of the four standard risk patients who relapsed, there were two CNS relapses, one systemic relapse and one testicular relapse. Two of the four have died, the remaining two (a CNS and the testes) are both disease-free at 15 months following retreatment.

Of the 11 increased risk patients who relapsed, five were in the CNS, five were systemic, and one was a combined simultaneous systemic and CNS relapse. Five are alive and six have died – all five deaths were in the group who relapsed systemically, and their survival from diagnosis ranged from

Table 2. Current analysis 6/1/1978

15 Relapses (of 50)	– 7 CNS – 6 Systemic – 1 CNS and Systemic – 1 Testes
Risk factor and relapse	– 11 (of 22) Increased Risk – 4 (of 28) Standard Risk
Time on study	– 22 to 68 Months
Median time on study	– 3 Months

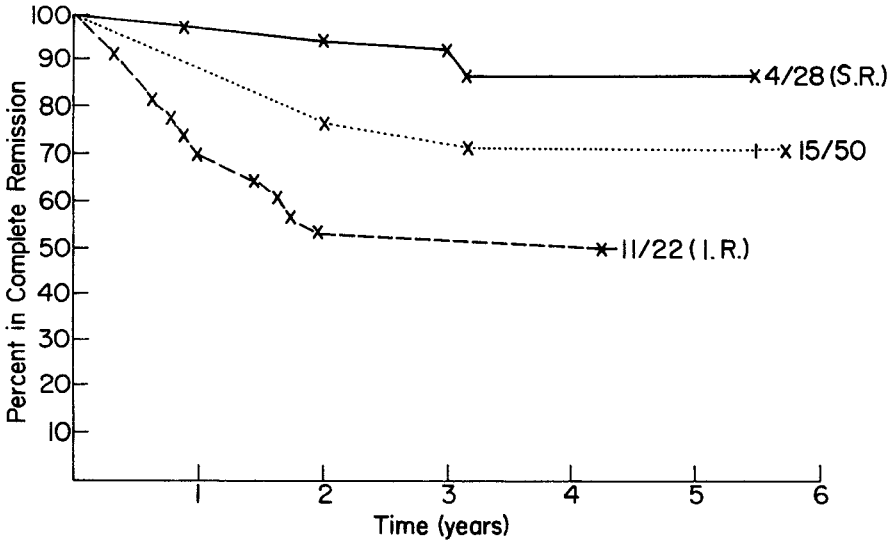

Fig. 2. Duration of complete remission employing IDM. The three curves are: Standard Risk Patients (top), Increased Risk Patients (bottom), and the Overall (middle)

9–17 months with a median of 12 months. Of the 5/11 patients at increased risk who suffered CNS relapse as the initial site of failure, 2/5 are currently disease-free at 33 and 9 months following retreatment.

One of the increased risk children who developed CNS leukemia was a 22-month-old male who presented with a central right facial palsy at diagnosis which subsequently disappeared with induction therapy and was thought to be due to CNS leukemia, but a spinal tap was not performed until two weeks later and there was no lymphoblasts in the CSF at this time. His CNS relapse occurred 23 months after diagnosis. A nine-year-old female who presented 48 months ago with frank papilledema was also thought to have CNS leukemia. The papilledema disappeared with induction therapy and again cytological confirmation from the CSF was lacking. She has remained in continuous complete sustained remission following the initial induction therapy.

Eight of the 50 children who entered complete remission have died and 84% currently remain alive with a median of 33 months after diagnosis (Fig. 3).

At present, of the 15 relapses, four have been successfully retreated and hopefully have a chance for cure. These four are comprised of three CNS relapses and one testicular relapse. Two were in the increased risk group and two in the standard risk group. Disease-free time intervals following retreatment in the CNS relapse group are 9, 17, and 33 months, and in the testicular relapse, 17 months. For CNS relapse, these patients were intensively retreated with steroids and Vincristine and IDM as before (i.e., 500 mg/m^2 on three occasions), but with simultaneous triple intraventricular chemotherapy through an Ommaya reservoir consisting of MTX at 12 mg/m^2 (maximal 15 mg/m^2), AraC at 25 mg/m^2, and Hydrocortisone at 6 mg/m^2 followed by maintenance intraventricular chemotherapy.

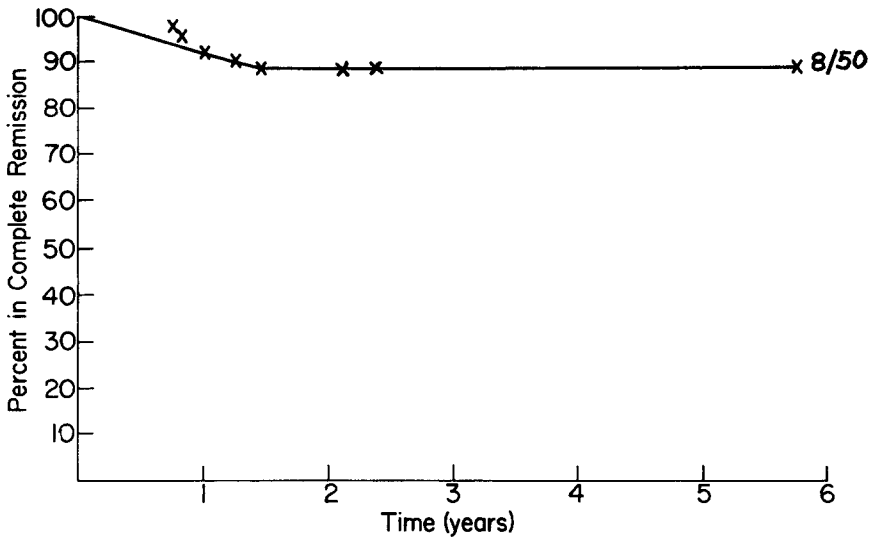

Fig. 3. Survival in 50 patients, treated with IDM, who achieved complete remission

Toxicity

The toxicity (Table 3) from the IDM included: 1. Vomiting occurring in 20/50 patients (40%) and was most pronounced during the first 2–4 hours after the institution of IDM, but occasionally persisting for 24–48 hours; 2. oral ulceration occurring in 20/50 patients (40%) with oral mucositis in 14 and pharyngitis in six patients. This was mild in 17/20, i.e., there were small ulcers which did not substantially interfere with oral intake and salivation; 3. hematologic toxicity occurring in 12 patients (24%) which, however, was minimal in its severity; there were no related clinical manifestations; 4. hepatic toxicity occurring in 11 patients (22%) as evidenced by increase of liver enzymes, particularly the SGOT. However, the peak SGOT was less than twice the normal level and returned to normal in all cases; and 5. transient maculopopular rashes occurring in three cases (6%) and lasting for several days. No case of renal toxicity was noted.

Table 3. Toxicity

Vomiting (with administration)	20/50	
Hematological		
WBC	2 ($<3000/mm^3$)	0 ($<1500/mm^3$)
Hgb	10 (<10 gm%)	0 (<8 gm%)
Platelets	0 ($<100000/mm^3$)	
Mucositis	14/50 (3 moderate and 11 mild)	
Pharyngitis	6/50	
Hepatic	11/50 (mild)	
Skin	3/50	
Renal	0/50	

The overall regimen has been very well tolerated. There has been no life-threatening toxicity and no deaths secondary to IDM. Furthermore, there have been no cases of leukoencephalopathy and no interstitial pneumonia associated with IDM. One adolescent experienced anaphylaxis with the first dose of L-Asparaginase. There have been neither infectious deaths nor toxic deaths for any patient while in remission on this study.

Discussion

This study was clinically based on the early work of Djerassi who demonstrated the effectiveness of high doses of MTX in ALL [10]. CALGB Protocol 6601 demonstrated that the greatest proportion of children remaining in complete remission were those who received the intensive cycles of IV MTX (18 mg/m^2) daily for five days every two weeks (i.e., they received 90 mg/m^2 as a total dose every two weeks) and reinduction pulses of Vincristine and Prednisone for a period of eight months [4]. In addition, CALGB Protocol 6801 demonstrated that "prophylactic" IT MTX during induction was important in preventing overt CNS leukemia [4]. Furthermore, Haghbin, et al. reported data suggesting that intensive systemic chemotherapy may decrease the incidence of CNS leukemia [11].

This study was pharmacologically based on the following: 1. Reports showing that IV IDM resulted in MTX levels of 10^{-7} M reaching the CNS axis and diffusing into the CSF [9]; 2. the studies of Oldendorf and Danson [12] using C^{14} sucrose in rabbits and Bourke, et al. [13] using C^{14}-5-fluro-uracil in monkeys demonstrated that the concomitant use of intrathecal with intravenous injection led to higher levels of drug in the CSF and more even distribution throughout the CNS than with either method alone, and the findings that when MTX is given only via lumbar puncture the distribution of MTX throughout the CSF is very variable [14]. Studies in man corroborate these animal observations, i.e., higher levels of CSF MTX are obtained with concomitant administration of IT and IV MTX than with either technique alone [14]. Thus, the technique employed in the present study of simultaneous IDM plus IT MTX enables one to more effectively bathe the CNS axis; and 3. the MTX levels following 500 mg/m^2 for 24 hours remain at 10^{-5} M in the serum for the 24-hour infusion period [9, 15]. It is thought that such levels will effectively "hit" leukemic cells in other potential sanctuaries such as the gonads, etc.

In large part, the clinical objectives of this study have been attained. Only 2/28 standard risk patients developed CNS leukemia (7%) and 7/50 of the entire population experienced this complication (14%). A recent study of children treated with prophylactic cranial RT and IT MTX or IT Cytosine Arabinoside showed that 53% developed abnormal findings as detected by computerized tomography (CT) [16]. These findings included: dilated ventricles, intracerebral calcifications, demyelination and dilation of subarachnoid space. Furthermore, a reduction in growth hormone secretion in children treated with prophylactic cranial RT has also been reported [17].

A comparable CT scan study has been undertaken in our population and only one child of 43 studied was clearly abnormal. This child presented with papilledema and probably had CNS leukemia at the time of diagnosis and demonstrated mild ventricular dilatation, but no calcification and no decreased attenuation coefficient was seen in any of the 43 cases.

The overall relapse rate in this study is 15/50 (30%) and the CNS relapse rate as the initial site of failure is 7/50 (14%). Thus, 7/15 relapses occurred in the CNS. This proportion is higher than that seen in studies where children received cranial RT plus IT MTX [18] or IT MTX alone because the systemic control is excellent. One possible explanation is that IDM is more effective in eradicating systemic leukemic rests in such areas as gonads, bone marrow, and liver.

Only one male child (1/25) developed testicular relapse. We attribute this to intensifying systemic therapy with IDM which presumably can eradicate disease in sanctuary sites such as liver, spleen and gonads.

A large study (CALGB Protocol 7111) recently reported by Jones [19] has demonstrated a protective value of cranial RT and IT MTX over IT MTX alone in preventing CNS leukemia, but no benefit in the overall complete remission rate. This was the result of an increased incidence of hematological relapse in the patients who received cranial RT. The British Medical Research Council also has observed a higher rate of hematological relapse in these patients receiving prophylactic craniospinal radiation than in those without CNS prophylaxis [20]. In the British study, the radiation-treated group, either cranial or craniospinal, had a greater lymphopenia which may reflect a perturbation of the immune system and thus lead to a greater systemic relapse [21,22].

The toxicity from IDM was minimal and easily tolerated. The control of bone marrow relapse (1/28) in standard risk patients, and in the entire population, 7/50 of the patients with ALL under observation through 68 months, is excellent (Fig. 3), The absence to date of CNS complications from this form of therapy, particularly when compared to the complications of cranial RT [16,17,23–25] are of great importance to children now being cured of this disease.

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