EFFICACY OF INTRATHECAL METHOTREXATE WITH AND WITHOUT CRANIAL RADIOTHERAPY IN PREVENTING CENTRAL NERVOUS SYSTEM RELAPSES IN ACUTE LYMPHOCYTIC LEUKEMIA

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ABSTRACT

Introduction of CNS chemoprophylaxis was a major milestone in the development of current therapy for acute lymphocytic leukemia. However, controversies are still existing for ideal form of CNS chemoprophylaxis. The present study was conducted to determine the efficacy of intrathecal methotrexate (IT-MTX) with and without cranial radiotherapy in preventing CNS relapses in Indian children. CNS chemoprophylaxis comprising of six injections of intrathecal methotrexate (12 mg/M^2) was administered alone or along with cranial radiotherapy (2000 GY) in 76 children each after successful induction remission. Cranial radiotherapy (RT) with intrathecal methotrexate (IT-MTX) was observed to be more effective as CNS relapses were seen in 11.8% of children as compared to 16.8% of children receiving IT-MTX alone. IT-MTX alongwith cranial RT delayed the occurrence of CNS relapses and prolonged the event free survival periods.

Key words: *Acute lymphoblastic leukemia, Chemotherapy, Radiotherapy, Intrathecal methotrexate.*

The introduction of central nervous system (CNS) prophylaxis was an important milestone in improving the event free survival period in children with acute lymphocytic leukemia (ALL)(1-4).

CNS relapses have been observed between 41-75% of cases prior to the introduction of CNS prophylaxis(5). Over 60% of Indian children have one or more poor prognostic factors at diagnosis(6). T cell leukemia was observed in over 35% of these children(7). Long term event free survival results are likely to be poorer in presence of poor risk factors in over 60% of Indian children at diagnosis. In the present study we have evaluated the efficacy of intrathecal methotrexate with and without cranial radiotherapy (RT) in preventing CNS relapses in these children.

Material and Methods

Children with acute lymphocytic leukemia (ALL) who have achieved successful induction remission following AIIMS protocols between 1972 and 1987 were the subjects of the present study. Patients who had received chemotherapy prior to admission to AIIMS were excluded from the present study. Children who had CNS involvement at diagnosis were also excluded for the purpose of the present study. One hundred and fifty two children achieved complete remission following one of the four induction regimens (*Table I*).

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Diagnosis of ALL was made in the presence of predominance of lymphoblasts or stem cell (over 40% of cells) in the bone marrow. In each case, cytochemistry studies were done to confirm that blast cells were that of lymphoid origin. Morphology of lymphoblastic cells were subclassified as per the FAB system(8). Diagnosis of CNS leukemia was excluded when blast cells were not observed in a centrifuged CSF sample after Wright's staining. CSF biochemistry and cultures were also under-

TABLE I—*Outline of Therapeutic Regimens*

Induction therapy drug		Dose/Route	Days of administration
Regime I	Prednisolone	60 mg/M^2/day PO	Day 1 to day 28
	+		
	6-Mercaptopurine	60 mg/M^2/day PO	Day 1 to day 28
Regime II	Prednisolone	60 mg/M^2/day PO	Day 1 to day 28
	+		
	Vincristine	1.5 mg/M^2/day IV	Days 1,7,14,21
Regime III	Prednisolone	60 mg/M^2/day PO	Day 1 to day 28
	+		
	Vincristine	1.5 mg/M^2/day IV	Days 1,7,14,21
	+		
	L-Asparaginase	10,000 IV/M^2/day	Days 2,8,15,22
Regime IV	Prednisolone	60 mg/M^2/day PO	Day 1 to day 28
	+		
	Vincristine	1.5 mg/M^2/day IV	Days 1,7,14,21
	+		
	Adriamycin	30 mg/M^2/day IV	Days 1,7,14,21
Consolidation Therapy (In Regime IV): Started After Bone Marrow Remission			
	Cyclophosphamide	1000 mg/M^2/day IV	Days 1,15
	L-Asparaginase	6000 IV/M^2/day IM	Days 2,4,6,8,10,12,14
CNS Prophylaxis (For ALL regimes) Started After proven Bone Marrow Remission			
Group A: Methotrexate		15 mg/M^2/day IT	Days 1,5,8,12,15,18
Group B: Methotrexate		15 mg/M^2/day IT	Days 1,5,8,12,15,18
	+		
	Cranial Radiotherapy	2000 GY	Over 2 weeks
Maintenance Therapy (for ALL regimes)			
6-Mercaptopurine		60 mg/M^2/day PO	Daily
Methotrexate		20 mg/M^2/day PO	Once a week
Cyclic Therapy Regimen (in regime IV) Once Every 16 weeks			
Prednisolone		40 mg/M^2/day PO	Day 1-21
Vincristine		1.5 mg/M^2/day IV	Day 1,7,15

taken. Other investigations at diagnosis included liver and renal function studies. Cultures of blood, urine, throat, pus points were undertaken whenever these children developed fever. Blood counts were monitored regularly. Successful remission was defined when blast cells were less than 5% on bone marrow and biopsy. Consolidation and regular maintenance therapy was administered as per protocol. In the event of hamatological or other relapse, CSF was routinely examined. CSF examination was also undertaken on suspicion whenever indicated to detect CNS relapse. Bone marrow was examined at the first sign of CNS relapse.

Therapeutic regimens: An outline of therapeutic regimens of various AIIMS protocol is given in *Table I*. These protocols were developed depending upon the availability of the drugs and facilities at AIIMS. Prognosis and outcome of treatment plan was explained to the patients and their consent was obtained before initiating therapy in each case. Patients who achieved successful remission on one of the four regimens were analysed depending upon the type of CNS chemoprophylaxis. Group A (n = 76) patients received 6 biweekly injections of intrathecal methotrexate (ITT-MTX), while group B (76 children) received rediotherapy (RT) 2000 Rads along with IT-MTX as described above.

Children in both groups were administered maintenance therapy with 6 mercaptopurine daily and oral methotrexate weekly, regularly as per protocols. Dosages of these drugs were so adjusted to maintain the total counts between 2500-3000/μl.

Results

The study group of 152 children included 113 boys and 39 girls. Their ages ranged between 1 to 13 years at diagnosis. The distribution of children in various regimens I, II, III, IV was 13, 35, 37 and 67, respectively. Age and sex distribution and prevalence of poor risk factors at diagnosis was comparable in two groups receiving different modes of CNS therapy (*Table II*) to determine the relative efficacy of the two modes of CNS therapy in preventing CNS leukemia and its effect on duration of event free survival period. Median event free survival period in these two groups A and B was 8 and 22 months, respectively. CNS relapse terminated event free survival in 13 of 76 (16.8%) patients of Group A and 9 of 76 (11.8%) in Group B children. Incidence of CNS relapses in two groups was not statistically significant. However, CNS relapses in the IT-MTX group (Group A) tended to occur earlier as in line of 13 (79%) children, CNS relapse had

TABLE II—*Distribution of Poor Risk Factors in Two Different CNS Prophylaxis Groups*

Factor	Group A IT-MTX+RT (n = 76) No.	Group B IT-MTX (n = 76) No.
1. Age <1 or >10 (years)	10	14
2. Male sex	59	54
3. TLC 50,000/μl	16	14
4. Platelets <20,000/μl	1	1
5. Liver >5cm	24	20
6. Spleen >5 cm	17	15
7. Significant lymphadenopathy	7	2
8. Hb>10 g/dl	4	6
9. Mediastinal mass	4	4
10. L_2/L_3 morphology	15	12

occurred within first 12 months as compared to 2 of 9 (22%) children in Group B who developed CNS relapses in the same period.

Discussion

Emergence of CNS relapse in 20-70% of the cases(8,9) lead to the belief that there is subclinical involvement of the CNS at diagnosis. Pinkel and his colleagues believed that CNS acts as a sanctuary site where leukemic cells present at diagnosis escape from the effect of chemotherapeutic agents because of the blood brain barrier(1). Leukemic cells proliferate there and later manifest as CNS leukemia. He postulated that CNS prophylaxis will eradicate the leukemic cells and CNS relapses will be prevented. Introduction of CNS chemoprophylaxis later proved to be turning point in improving long term survival in ALL. CNS relapse is often associated with considerable morbidity, mortality and these children respond poorly to therapy(10-12). CNS relapse often terminates in hematological relapse(9). Various modes of CNS prophylaxis in use are IT-MTX alone or in combination with cranial RT, triple IT therapy during induction and maintenance therapy and high or intermediate dose of intravenous methotrexate either alone or in combination with IT-MTX(13). In earlier studies IT-MTX along with craniospinal cranial radiation was found to be superior than IT-MTX alone(14).

At Saint Jude Children's Research Hospital (SJCRH) CNS relapses were brought down to less than 10% with introduction of standard cranial RT (SJCRH study V) compared to 41-59% in their previous studies(15-17). In the SJCRH study VIII, CNS relapse was observed to be as low as 1.5% in children who received cranial RT along with standard maintenance therapy. The CNS relapse rate at various centres using IT-MTX alone or in combination with radiotherapy has been compared in *Table III*(18-23).

Over 60% of Indian children had one or more of poor prognostic factors at diagnosis. Presence of poor prognostic factor at diagnosis in such a high proportion of children indicate the aggressive biological behavior of leukemic cells in these children. Effectiveness of CNS chemoprophylaxis has been studied in population where the prevalence of poor risk factors is not as high as in Indian children (*Table III*)(18-23). The present study has evaluated the efficacy of CNS chemoprophylaxis in children with high prevalence of poor risk factors at diagnosis.

CNS relapses were less frequent in the irradiated group as compared to children who received IT-MTX alone. However, median event free survival in the irradiated group was 22 months while it was only 8 months in the IT-MTX group.

Possibility of a still higher CNS relapse rate in Group II children is likely as the median event free survival period is significantly shorter in these children. Present study confirms that effective CNS chemoprophylaxis delayed the occurrence of CNS relapses. CNS relapses are expected to increase further with the increase in event free survival periods. High rate of CNS relapses in our children may be due to higher prevalence of poor risk factors at diagnosis. Thus there is a need to develop and evaluate alternative modes of CNS chemoprophylaxis in order to further decrease CNS relapse rate in Indian children with higher proportion of poor risk factors at diagnosis.

High dose IV-MTX has been found to be as effective as cranial RT with IT-MTX in reducing CNS relapses(24). The Pediat-

TABLE III—*CNS Relapse Rates Following CNS Chemoprophylaxis with IT-MTX Alone and IT-MTX+RT*

Study	Reference No.	No. of children	CNS relapse per cent
Chemoprophylaxis following IT-MTX			
CCSG-101	21	115	43
MSKCC-L-2	23	75	6.6
MSKCC-L-10	23	58	6.8
Present study		76	16.8
Chemoprophylaxis following IT-MTX+RT			
SJCRH-V	15	31	10
SJCRH-V14	3	45	4.4
SJCRH-VII	18	45	6.6
SJCRH-VIII	19	282	1.5
CCSG-141	22	574	6.0
CCSG-7420	20	105	4.8
SFCI-7301	21	SR 57	0
		HR 46	4.0
Present study		76	11.8

CCSG: Children's Cancer Study Group, MSKCC: Memorial Sloan-Kettering Cancer Centre, SJCRH = Sint Jude Children Research Hospital, POG = Pediatric Oncology Group, SR = Standard Risk, HR = High Risk, SFCI = Sidney Farber Cancer Institute.

ric Oncology group (POG) observed CNS relapses between 1.5 to 5% of cases following triple IT chemotherapy during induction, consolidation and maintenance therapy(25,26). This mode of CNS prophylaxis may be more suitable in our population as it avoids the adverse effects of radiotherapy and it can be administered in Institution where facilities for radiotherapy are not available.

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