

Intermediate Dose Methotrexate Versus Cranial Irradiation for Central Nervous System (C.N.S.) Prophylaxis in High Risk Childhood Acute Lymphoblastic Leukaemia (A.L.L.)

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ABSTRACT

The use of cranial irradiation for central nervous system prophylaxis in acute lymphoblastic leukaemia had been debated due to its long term neurotoxicity. An alternative method of prophylaxis using different doses of systemic methotrexate and an extended intrathecal chemotherapy are now being tried. This study is a retrospective analysis of treatment results of forty-six newly diagnosed pediatric acute lymphoblastic leukaemia patients presented to Abul Reesh Pediatric Hospital and referred to the oncology department of Kasr El-Aini Hospital, Cairo University, during the period from February 1994 until August 1997. Two different methods of central nervous system prophylaxis were applied, the first method (group I) was applied on 15 patients where an intermediate dose of systemic methotrexate (200 mg/m² I.V. shot followed by 800 mg/m² I.V. 24 hour infusion) was given for 6 doses (separated by 3 weeks intervals) together with triple intrathecal chemotherapy for 5 doses during the consolidation phase and followed by another 5 doses during maintenance phase. The second method (group II) was applied on 31 patients where whole cranial irradiation was given at radiation dose of 1800c Gy in 10 treatments over two weeks using Cobalt 60 machine and intrathecal chemotherapy was given only for 3 times during induction. By the end of January 1999, full analysis of clinical data of both groups of patients was done, where they were found to be comparable as regards their age, sex, time before clinical presentation, clinical symptoms and signs and haematological profiles. After a median follow up of 25 months, the two groups of patients were not statistically different as regards their complete remission rate (100% in group I and 96.7% in group II), isolated central nervous system relapse rate [1/15 (6.7%) in group I and 2/31 (6.5%) in group II], isolated systemic relapse rate [3/15 (20%) in group I and 11/31 (35.5%) in group II] and combined systemic and central nervous system relapse rates [2/15 (13.3%) in group I and 3/31 (9.7%) in group II]. As regards survival figures, the two groups were not statistically different either in their 2-year isolated central nervous system relapse free survival rates (90% in group I and 87% in group II),

their 2-year isolated systemic relapse free survival rates (85.7% in group I and 60% in group II) or combined central nervous system and systemic relapse free survival rates (83.3% in group I and 90% in group II) as regards event free survival rates. The 2-year event-free survival rate for group (I) was 64.3% versus 47% for group II the result being statistically insignificant. As regards overall survival rates, the 2-year survival rate was 73.3% for group I versus 48.2% for group II the result being statistically insignificant.

Conclusion: Both modalities offer the same central nervous system prophylactic effect.

Key Words: Pediatric - Acute lymphoblastic leukaemia - C.N.S prophylaxis.

INTRODUCTION

A major advance in the treatment of acute lymphoblastic leukaemia (ALL) was the recognition that specific therapy directed at the central nervous system (CNS) reduced the likelihood of subsequent relapse [27,28]. For nearly 20 years, irradiation to the cranium or craniospinal axis was recognized as the most effective form of presymptomatic central nervous system prophylaxis [3,10]. However, as survival improved, the long-term neurotoxicity of cranial irradiation raised the concerns about such manoeuvre [18,20]. Children receiving cranial irradiation were found to have diminished intelligence and academic achievement if compared to children receiving other central nervous system therapies [15-17,32]. This led to studies exploring the role of systemic and/or intrathecal methotrexate as a substitute of cranial irradiation for C.N.S. prophylaxis in acute lympho-

blastic leukaemia [14,30]. Long term follow up of acute lymphoblastic leukaemia cases revealed the fact that high risk ALL patients had a significantly higher incidence of C.N.S. relapse if compared to average or low risk ALL cases [8,9,11]. For this reason, this study was carried out retrospectively on high risk ALL cases to compare the efficacy of systemic intermediate dose methotrexate combined with extended triple intrathecal chemotherapy versus whole cranial irradiation as two different modalities for central nervous system prophylaxis through comparative analysis of isolated central nervous system relapse rates and their relapse free survival rates in the two groups of patients.

PATIENTS AND METHODS

This is a retrospective study carried out on 46 newly diagnosed cases of high risk childhood acute lymphoblastic leukaemia (ALL) referred from the pediatric clinic of Abul-Reesh Hospital to the department of clinical oncology and nuclear medicine, Cairo University during the period February 1994 till August 1997.

Pretreatment evaluation:

At initial presentation, all patients were clinically assessed by history and full physical examination. Laboratory investigations included a differential blood count, bone marrow examination with special stains for leukaemia, renal and hepatic assays, lactic dehydrogenase (L.D.H.) and cerebrospinal fluid (C.S.F.) cytology. Radiological assessment was done by doing a chest X-ray and abdominal ultrasound.

Protocol schema:

I- Induction of complete remission was similar in the two groups and its schedule is shown in table (1).

Bone marrow examination was carried on 29 patients in complete clinical and haematological remission who were submitted to the other two phases of treatment.

II- Consolidation and C.N.S. prophylaxis: this phase is shown in table (3) (for group I).

III- Maintenance phase:

In group (I) maintenance treatment was given for 105 weeks. The drugs used in maintenance treatment were a combination of 6-mercaptopurine and purinethol with triple intrathecal chemotherapy together with reduction

chemotherapy using vincristine and prednisone (Table 4).

In group II, maintenance treatment was given for 130 weeks with a combination of 6-mercaptopurine and purinethol together with re-induction chemotherapy in the form of vincristine and prednisone (Table 5).

In group II, C.N.S. prophylaxis was achieved by both triple intrathecal chemotherapy given during the induction phase (day 1, 12 and 19), as well as by radiation therapy given immediately after achieving complete remission through whole cranial irradiation using two parallel opposed radiation beams including the whole skull with strict inclusion of skull base down to second cervical spinous process (potential sites of infiltration by malignant leukaemic cells which correspond to an exit site of different cranial nerves from the brain).

The total dose of radiation was 1800 cGy given in 10 treatments over a total period of two weeks (Five days a week). The radiation therapy machine is Cobalt 60 giving radiation therapy at 80 cm source skin distance.

The criteria of selection of patients to either type of C.N.S. prophylaxis are not known, but may be due to physician selection where some physicians prefer one type of C.N.S. prophylaxis or it may be due to time period selection.

Statistical methods:

Median and range were used for describing quantitative data and proportion for qualitative data.

- Mean Whitney test was used for comparison of medians.
- Chi-square and Fisher exact tests were used for comparison of proportions.
- Kaplan Meier test was used for estimating survival and log-rank test for comparing survival curves [25].

RESULTS

As of January 1999, the median follow up of both groups of patients was 25 months. The clinical criteria of both groups of patients are shown in table (6).

Fifteen patients (32.6%) of the total were submitted to arm I, while 31 cases (67.4%) were submitted to arm II. Complete remission

(C.R.) rate was achieved in 45 patients (97.8%) of the total, while one patient (2.2%) did not enter into C.R. The C.R. rate was 100% in group I, while it was 96.7% in group II, with a non-significant difference ($p = 0.4$).

The mean number of infection episodes during the whole treatment period was 4 times (S.D. = 2.5) in all patients. In group I, the mean number of infection episodes was 4 and it affected 8 cases (53.33%) of group I while in group II, it affected 15 cases (48.38%), at a mean of 5 times, a non significant difference ($p = 0.4$).

The number of bleeding episodes during the whole treatment period was at a mean of 0.7 time (S.D. 0.98) in all cases, in group I, it was at a mean of one time and it affected 8 cases (53.3%) while, in group II, the mean number was one time and it affected 18 cases (54.8%), a statistically insignificant difference.

Isolated C.N.S. relapse was observed in a total number of 3 cases (6.5%). In group I, it occurred in one case only (6.7%) and in group II, it affected two cases (6.5%), a statistically insignificant difference ($p = 0.45$). Systemic relapse was observed in a total of 19 cases (41.3%) and it occurred in 5 patients in group I (33.3%), while in group II, it occurred in 11 cases (45.2%), the difference was not statistically significant ($p = 0.5$). Combined systemic relapse occurred in 5 cases, it occurred in 2 cases in group I (12.5%), while it occurred in 3 cases of group II (13.4%). The difference was not statistically significant ($p = 0.5$).

The overall survival of both study groups showed that the 3 year overall survival for (group I) was 60% while the 3 year overall survival for (group II) was 48.2%, a statistically insignificant difference ($p = 0.39$) Fig. (1).

The event-free survival of both study groups showed that the 3 year event free survival was 57.1% for (group I), 47% for (group II), a statistically insignificant difference (p value = 0.44) Fig. (2).

The estimated 3 year isolated relapse rate including both systemic and C.N.S. relapses occurring to the same patients was 83.3% for (group I) and 90% for (group II), a statistically insignificant difference ($p = 0.63$) Fig. (3).

The estimated 3-year isolated C.N.S. relapse free survival was 90% in (group I) and 87% in (group II), a statistically insignificant difference ($p = 0.74$) Fig. (4).

The estimated 3-year isolated systemic relapse free survival was 76.2% for (group I) and 60% for (group II), a statistically insignificant difference ($p = 0.29$) Fig. (5).

As regards laboratory findings, it was found that both groups of patients were not statistically different as regards their total leukocytic count (with a median count of 78,400/ μ l in group I and 38,000/ μ l in group II) ($p = 0.08$), their mean platelet count (with a mean of 88,000/ μ l in group I and 52,500/ μ l in group II) ($p = 0.10$), their bone marrow infiltration percentage by blast cells (a mean of 96.5% in group I and 89.6% in group II) French, American, British subtype where the majority of patients were of L2 subtype with group I having 15 cases (100%) and group II having 29 cases i.e. 93.58% ($p = 0.41$), L1 subtype was represented by one case in group II only (3.2%) and L3 by one case in group II only (3.2%).

The difference between groups I and II as regards their laboratory and radiologic features is shown in table (7).

Table (1): Phase I (induction of complete remission).

Drug	Dose/m ²	Route	Day							
			1	2	5	8	12	15	19	22
Vincristine	1.5 mg	I.V.	X			X		X		X
Prednisone	40 mg	Orally								
L-asparaginase	6000 I.U.	I.M.		X	X	X	X	X	X	
Methotrexate, Cytosar	Age-adjusted*	I.T.	X				X		X	
Hydrocortisone										

I.V.= Intravenous I.M.= Intramuscular I.T.= Intrathecal

*Age-adjusted dosage of triple intrathecal chemotherapy is shown in table (2).

Table (2): Age-adjusted dosage for triple intrathecal chemotherapy.

Age (in years)	< 2	> 2-3 <	> 3-8 <	> 8
Methotrexate dose (mg)	8	10	12	15
Cytosar dose (mg)	20	30	40	50
Hydrocortisone dose (mg)	8	10	12	15

Table (3): Consolidation and C.N.S. prophylaxis in group I.

Chemotherapy	Dose in mg/m ²	Route	Weeks														
			5	7	8	9	10	12	13	15	16	17	18	19	22	24	
Methotrexate Cytosar hydrocortisone	Age adjusted*	I.T.	x			x		x			x				x		
6-mercaptopurine	75	Oral															
Methotrexate followed by Methotrexate	200 800	I.V. shot 24 hour I.V. infusion	x				x			x				x			x
After 24 hours: Leucovorin	5**	Oral or I.V.															
Vincristine	1.5***	I.V. (D1+8)				x											x
Prednisone	40****	(D1→ 8)				x											x

*: See table (2) **: Dose given every 6 hours for 5 doses *: Maximum total dose 2mg. ****: Maximum total dose 60 mg.

Table (4): Maintenance phase for group (I).

Chemotherapy	Dose in mg/m ²	Route	Weeks														
			25	26	32	40	41	48	56	57	73	89	103	105			
6MP	75	Oral															
MTX	20	Oral or I.M.	Weekly														
VCR	1.5*	I.V. (D1+8)	x					x				x	x	x	x		
Prednisone	40**	Oral (D1→ 8)	x					x				x	x	x	x		
Triple chemotherapy (I.T.)	Age adjusted***	I.T.			x	x	x			x	x						

*: Maximum total dose 2 mg **: Maximum total dose 60 mg ***: See table (2).

Table (5): Maintenance and consolidation phase for group (II).

Chemotherapy	Dose in mg/m ²	Route	Weeks														
			7	19	31	43	55	67	79	91	103	115	127	130			
6MP	75	Oral															
MTX	20	Oral or I.M.	Weekly														
VCR	1.5*	I.V. (D1+8)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pred.	40**	Oral (D1→ 8)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

*: Maximum total dose 2 mg **: Maximum total dose 60 mg

Table (6): Clinical criteria of group I and group II patients.

Parameter	Group I		Group II		p-value
I- Total number of patients	15		31		
II- Age range (in years)	2-12		2-10.5		0.521
Median	5		6		
	No.	%	No.	%	
III- Sex:					
A- Male	8	53.3	19	31.3	0.603
B- Female	7	46.7	12	38.7	
IV- Symptoms:					
A- Fever	12	80	22	71	0.562
B- General weakness	12	80	19	61.3	0.201
C- Bleeding tendency	7	46.6	18	58	0.471
D- Abdominal discomfort	11	73.3	20	46	0.652
V- Signs:					
A- Pallor	12	80	21	67.7	0.383
B- Signs of bleeding	7	46.6	13	41.9	0.801
C- Peripheral lymphadenopathy	15	100	27	87	0.071
D- Mediastinal lymphadenopathy	1	6.7	4	12.9	0.871
E- Organomegaly	11	73.3	22	70.9	0.702
F- Bone tenderness	13	86.6	24	77.4	0.602
G- Testicular involvement	0	0	1	3.2	1.000

Table (7): The difference between group I and II in their laboratory and radiological features.

Parameter	Group I	Group II	p-value
I- Total number of patients	15	31	
II- Laboratory features: (median values)			
A- Total leucocytic count	78.500	38.00	0.81
Range (1µl)	(69-88)	(28-48)	
B- Blast percentage (%)	61.07	36.42	0.021
Range	(52-70)	(26-46.8)	
C- Hemoglobin content (g/dl)	6.2	7	0.010
Range	(4-8.2)	(5-9)	
D- Platelet count (/µl)	88.000	52.50	0.100
Range	(77-99)	(45-60)	
E- Bone marrow blast percentage (%)	96.5	89.6	0.211
Range	(95-98)	(80-99.2)	

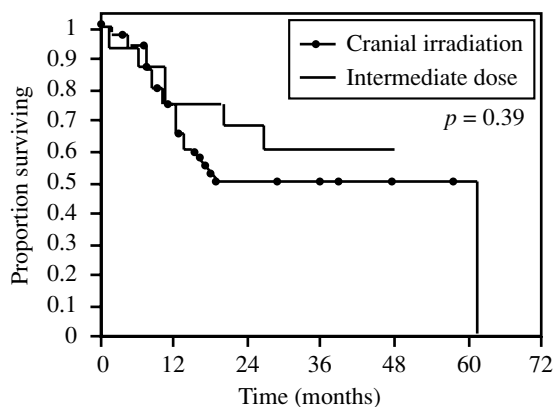


Fig. (1): Overall survival of both study groups.

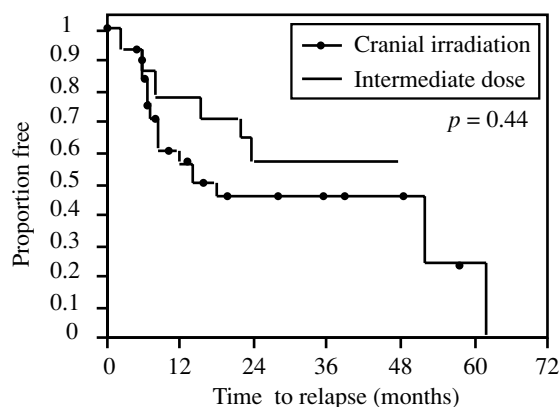


Fig. (2): Event-free survival of both study groups.

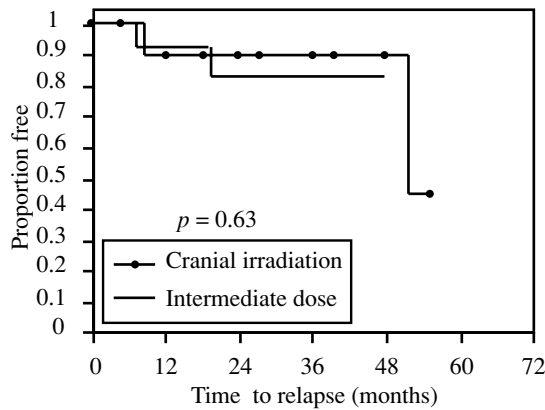


Fig. (3): Time to combined CNS and systemic relapse in both groups.

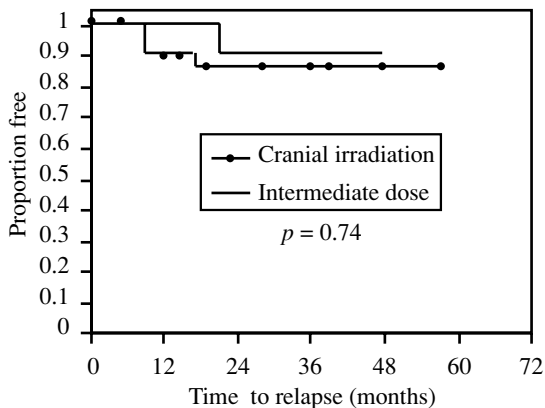


Fig. (4): Time to isolated CNS relapse in both groups.

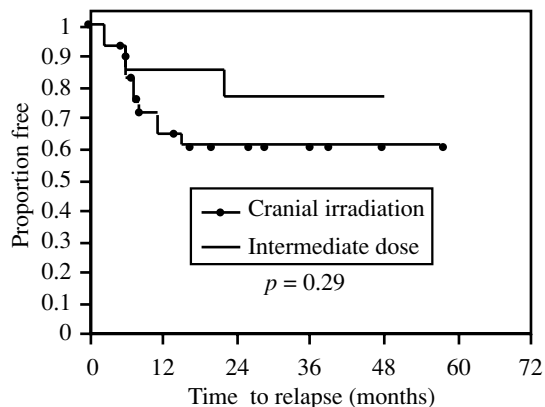


Fig. (5): Time to isolated systemic relapse in both groups.

DISCUSSION

Three methods are useful for prevention of meningeal leukaemia: (1) intrathecal injection of antileukaemia antimetabolites, with or without corticosteroids, (2) high dosage intravenous administration of antimetabolites sufficient to achieve therapeutic level in the C.S.F. and (3) radiation therapy.

The diffusion of drugs into perivascular leptomeninges is dependent on the flow of C.S.F. from the subarachnoid space, which is distant from arterioles and venules deep in the brain [24,26]. For this reason, radiation therapy early in remission was introduced for prevention of meningeal leukaemia [23]. Although, effective, cranial irradiation can result in several adverse sequelae including acute reactions (during the course of radiotherapy) like nausea, vomiting, blurring of vision and headache (manifestations of increased intra-cranial tension), subacute effects (6-8 weeks later) like fever and somnolence and late affects (several months to years later) like neuropsychological impairment, growth disturbances, leukoencephalopathy, cerebral microangiopathy and brain tumors [13,20,22,30-32]. However, one of the most important and interesting late sequelae of radiation therapy to the brain is development of brain tumors although their incidence is very rare [13]. Hence, the current goal is to achieve affective C.N.S. prophylaxis with minimizing neurotoxicity [6,19].

In the present study, the isolated C.N.S. relapse rate in children with ALL who did not receive cranial irradiation was 6.7%, while for the other group (receiving cranial irradiation), it was (6.5%), a statistically insignificant difference ($p = 0.45$).

Most of the studies done for assessment of different modalities of central nervous system prophylaxis in pediatric acute lymphoblastic leukaemia were based on a definite risk group of patients. So, low risk ALL cases were studied by Littman et al. [14] who compared cranial irradiation with extended intrathecal chemotherapy as C.N.S. prophylaxis and revealed a C.N.S. relapse rate of 6% for the first modality and 4% for the second. Pilot studies investigating the role of non irradiation modalities for C.N.S. prophylaxis in low risk ALL patients were performed by Camitta et al. [5] who reported an absence of C.N.S. relapse after an intermediate dose of I.V. methotrexate with extended intrathecal chemotherapy. On the other hand, 2% C.N.S. relapse rates have been reported by Krance et al. [12] after extended intrathecal chemotherapy.

Intermediate risk patients were studied by Tubergan et al. [31], who compared cranial irradiation to extended intrathecal chemotherapy and found a C.N.S. relapse rate of 7% and 9%,

respectively an insignificant difference ($p = 0.13$). Also, Dibar et al. [7] revealed a C.N.S. relapse rate of 4% after high dose I.V. methotrexate.

High risk ALL cases were studied by Abromowitch et al. [2] who compared cranial irradiation to high dose IV methotrexate and found relapse rates of 4% and 10%, respectively (in significant difference $p = 0.46$), 3 year event free survival rate of 60% for group (I), 51 for group (II), a statistically insignificant difference (p value = 0.44). As regards overall survival of both study groups, 3-year over all survival for group I was 64%, while it was 53% for group II, a statistically insignificant difference ($p = 0.39$).

A combination of an extended intrathecal chemotherapy and an intermediate dose of methotrexate was studied by Poplaek et al. [22] and Cemitta et al. [4] who found a C.N.S. relapse rate of 1% and 9%, respectively; 3-year event free survival rate of 70% for group I, 63% for group II; 3-year overall survival of 62% for group I while it was 57% for group II, a statistically insignificant difference ($p = 0.41$).

Krance et al. [12] reported a 4% C.N.S. relapse rate after a combination of intermediate dose methotrexate and systemic cytosar during maintenance phase.

In Egypt, Abdel Mokhales [1], in a prospective study of 194 new ALL cases, found a C.N.S. relapse rate of 7.4% in T cell ALL after high dose I.V. methotrexate and Ara-C infusion combined with extended intrathecal chemotherapy while no C.N.S. relapse had been demonstrated in B precursor ALL (using an intermediate dose I.V. methotrexate and Ara-C and extended intrathecal chemotherapy) or in B cell ALL (using high dose I.V. methotrexate, Ara-C infusion and extended intrathecal chemotherapy). As a whole, the C.N.S. relapse rate for all study groups was 2.3%.

These studies suggest that an adequate C.N.S. prophylaxis can be achieved successfully with modalities other than cranial irradiation taking into consideration a risk-directed treatment to achieve relatively lower C.N.S. relapse rates.

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