

## The Effect of Intensive Intrathecal Chemotherapy on Prognosis of Childhood Lymphoblastic Leukemia with Central Nervous System Involvement: A 20-Year Experience

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### Abstract

**Background:** Primary central nervous system involvement and central nervous system relapse are poor prognostic events in acute lymphoblastic leukemia. Due to severe skeletal and endocrine complications of craniospinal radiotherapy, only cranial radiotherapy is advisable. However only 15% of the cases with central nervous system relapse may remain in remission; a second central nervous system or bone marrow relapse is common. Prevention of central nervous system relapse is an extremely important way to decrease both mortality and morbidity in childhood leukemia.

**Methods:** This prospective study was conducted from June 1995 to May 2014. A total of 90 children diagnosed with acute lymphoblastic leukemia enrolled in this study following parental informed consent. There were 30 children with primary central nervous system involvement and 60 that had central nervous system relapse due to acute lymphoblastic leukemia. Patients were randomly divided into two groups: 30 patients in group A (control group) received triple intrathecal injections every 2 months according to high risk acute lymphoblastic leukemia protocols for a total of three years. Group A was divided into the following subgroups: A1 (primary central nervous system involvement; n=15) and A2 (central nervous system relapse; n=15). Group B (case group) comprised 60 patients that received additional triple intrathecal injections during the fourth and fifth years (2 years after discontinuation of maintenance chemotherapy). Group B was subdivided as follows: B1 (primary central nervous system involvement; n=20) and B2 (central nervous system relapse; n=40). For each patient in group A, two age and sex matched patients in group B were enrolled. Patients were followed for 2-15 years.

**Results:** From 15 patients in group A1 (control with primary central nervous system involvement), there were 5 central nervous system relapses, 3 bone marrow relapses, and 2 deaths. Boys had more relapses and deaths than girls (chi square: 15.63;  $P<0.001$ ). The majority of relapses occurred during the third to fifth years. In group A2 (control group with central nervous system relapse), from 15 patients, there were 7 with second central nervous system relapses, 6 with bone marrow relapses, and 2 deaths. The majority of relapses occurred during the third to fifth years. Boys had more relapses and deaths ( $P<0.005$ ). From 20 patients in group B1 (cases with primary central nervous system involvement) only 2 boys had central nervous system relapses. There were no bone marrow relapses and no male patients died. No relapse or deaths occurred in female patients (Fisher's exact test:  $P<0.001$ ). In group B2 (cases with CNS relapse): 8/40 patients had second central nervous system relapses; 3 had bone marrow relapse; and 2 died ( $P<0.003$ ). Most relapses occurred during the third to fifth years of maintenance therapy. Overall, boys in groups B1 and B2 had less mortality and morbidity (chi square: 27.6;  $P<0.001$ ) and better prognosis.

**Conclusion:** Extended intrathecal injections after discontinuation of maintenance chemotherapy is advisable for cases with primary central nervous system involvement and central nervous system relapses. However, we propose that national and international studies with greater number of patients should be conducted.

**Keywords:** Childhood leukemia, CNS involvement, CNS relapse, CNS prophylaxis, prognosis

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## Introduction

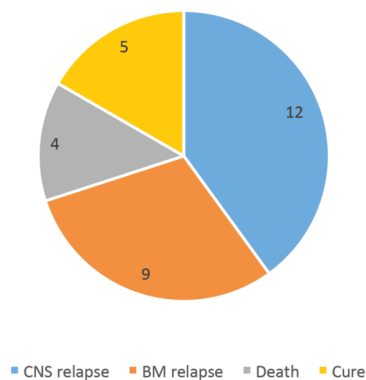
Although there are new protocols for acute lymphoblastic leukemia (ALL) treatment, the control of central nervous system (CNS) leukemia remains a therapeutic challenge in childhood ALL,<sup>1</sup> partly because of late complications that arise from cranial irradiation. With current approaches, approximately 2% to 10% of patients can be expected to develop CNS relapse.<sup>1</sup> Central nervous system relapse remains a major obstacle to cure, accounting for 30% to 40% of initial relapses in some clinical trials.<sup>1</sup> Inadequate control of CNS leukemia is partly related to the decreased use of cranial irradiation for subclinical disease in order to avoid long-term sequelae of this treatment modality such as poor school performance and endocrine complications. However, only 15% of CNS relapse cases may remain in remission and either a second CNS relapse or bone marrow (BM) relapse is usual. Attempts have been made to reduce the dose of therapeutic cranial irradiation in those with CNS leukemia at diagnosis or relapse. Most contemporary protocols do not specify cranial irradiation for infants or very young children, even if they present with CNS leukemia.<sup>2</sup> Prevention of CNS relapse is an important way to decrease both mortality and morbidity in childhood leukemia. Innovative treatment options are needed for children with primary CNS involvement, those who develop CNS relapses after a short initial remission, or after

cranial irradiation. The risk of a second CNS relapse or BM relapse is high and the cure rate is very low due to multiple drug resistance.

## Materials and Methods

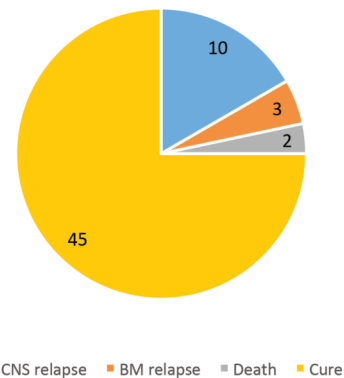
We conducted this prospective study from June 1995 to May 2014. There were 30 children diagnosed with ALL that had CNS involvement and 60 ALL children with CNS relapse enrolled in the study. We randomly divided the patients into two groups: 30 patients in group A (control group) that received triple intrathecal (IT) injections every 2 months according to the high risk ALL protocols for a three-year period. This group was subdivided as follows: A1 group (control patients with primary CNS involvement; n=15) and A2 group (control patients with CNS relapse; n=15). Group B (case group; n=60) received additional triple IT injections during the fourth and fifth years (2 years after discontinuation of maintenance chemotherapy). This group was subdivided, as follows: B1 (primary CNS involvement; n=20) and B2 (CNS Relapse) (n=40). Each patient in group A had two age and sex matched patients in group B. Patients were followed for 2-15 years. Each patient with primary CNS involvement or CNS relapse received cranial radiotherapy after at least 6 IT triple injections (methotrexate, hydrocortisone and cytarabine) in the first month of chemotherapy.

Control group: Standard IT therapy



**Figure 1.** Outcome of 30 patients in the control group that received standard triple intrathecal (IT) chemotherapy. CNS: Central nervous system; BM: Bone marrow.

Case group: Extended IT therapy



**Figure 2.** Outcome of 60 case group patients that received extended triple intrathecal (IT) chemotherapy. CNS: Central nervous system; BM: Bone marrow.

### Ethical approval

All procedures performed in this study were in accordance with the ethical standards of Shiraz University of Medical Sciences Research Ethics Committee and conducted according to the Declaration of Helsinki standards. Informed consent was obtained from parents of all patients included in this study.

### Results

This single institution prospective study enrolled 90 children with a mean age of  $7.8 \pm 3.6$  years. There were 20 boys and 10 girls in the control group. The case group consisted of 30 boys and 30 girls. Patients were followed for 2-15 years, with a mean follow up of 8 years (Table 1). Group A1 (control group with primary CNS relapse) had 5/15 CNS relapses, 3/15 BM relapses and 2/15 deaths. Boys had more relapses and deaths than girls (chi square: 15.63,  $P < 0.001$ ). Most relapses occurred in the third to fifth years of maintenance therapy (Figure 1). In group A2 (control group with CNS relapse) there were 7/15 second CNS relapses, 6/15 BM relapses, and 2/15 deaths. Most relapses occurred in boys during the third to fifth years. In this group, boys had more relapses and deaths ( $P < 0.005$ ). In group B1 (cases with primary CNS involvement) only 2/20 boys had CNS relapses, however there were no BM relapses or deaths in this group. No relapses or deaths occurred in girls (Fisher exact test:

$P < 0.001$ ; Figure 2). In group B2 (cases with CNS relapse), there were 8/40 with second CNS relapses; 3/40 had BM relapse, and 2/40 deaths ( $P < 0.003$ ; Figure 3). Most relapses occurred in the third to fifth years of maintenance therapy. Overall, boys in groups B1 and B2 had less mortality and morbidity (chi square: 27.6,  $P < 0.001$ ) and better prognosis (Table 2).

### Discussion

More effective chemotherapy is needed for patients with primary CNS involvement, CNS relapse, or for those who have a very high risk of developing this complication. Treatment strategies that can improve outcome in these subgroups include frequent and early IT therapy as used for Burkett's leukemia/lymphoma and IT liposomal cytarabine, which can maintain a therapeutic level of cytarabine in cerebrospinal fluid for two weeks or longer.<sup>1</sup> Precise assessment of the CNS relapse hazard is critical to avoid over- or under treatment of patients. Presenting features associated with an increased risk of CNS relapse in pediatric patients include a T-cell immunophenotype, hyperleukocytosis, high-risk genetic abnormalities such as the Philadelphia chromosome and t(4;11), as well as the presence of leukemic cells in cerebrospinal fluid that may occur from iatrogenic introduction due to a traumatic lumbar puncture.<sup>2</sup> It is well recognized that the impact of many prognostic factors can be lessened or eliminated altogether

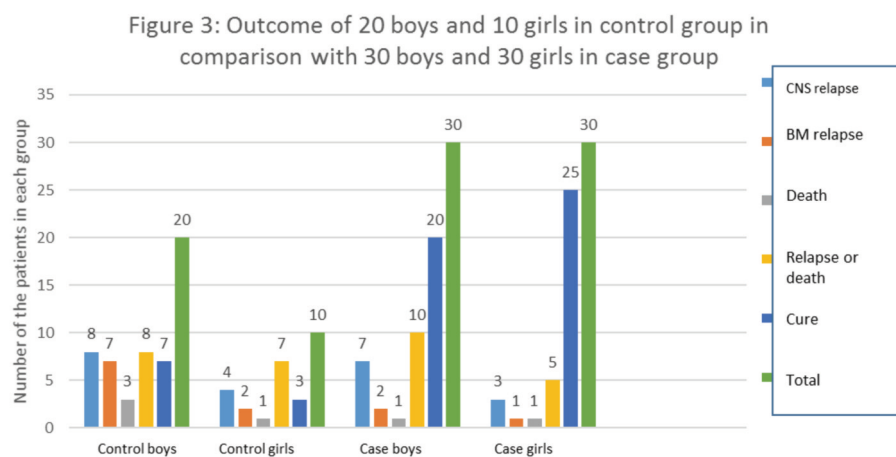


Figure 3. Outcome of control group (20 boys, 10 girls) compared with case group (30 boys, 30 girls) in terms of gender.

**Table 1.** Comparison between groups regardless of sex for impact of extended CNS prophylaxis in pediatric acute lymphoblastic leukemia (ALL) cases with primary central nervous system (CNS) involvement or CNS relapse.

Outcome	CNS Relapse	BM Relapse	Death	Relapse or death	Cure	Total	Statistical analysis method	P-value
<b>Groups</b>								
A (Control)	12	9	4	25(83.3%)	5(16.7%)	30	Chi square:27.63	<0.001
B (Case)	10	3	2	15(25%)	45(75%)	60		
Total	22	12	6	40(44.4%)	50(55.6%)	90		

BM: Bone marrow. Data from 20 years (1995-2014) of experience at Shiraz University of Medical Sciences. Note: Chi square was calculated for the final event (cure versus relapse or death).

with intensified treatment. For example, an association between the presence of leukemic cells in a cerebrospinal fluid sample that contains fewer than 5 WBC with an increased risk of CNS relapse has been shown in a number of clinical trials,<sup>3,4</sup> apparently because of differences in the efficacy of systemic and CNS-directed therapy among the study groups. Likewise, the increased risk of CNS relapse and poor event-free survival associated with traumatic lumbar puncture with blasts in cerebrospinal fluid can be overcome by more effective therapy.<sup>4</sup> Therefore, identification of primary CNS involvement or traumatic lumbar puncture with blasts warrants intensification of therapy to reduce the risk of CNS relapse in these patients. Patients with T-cell ALL and a presenting leukocyte count of more than  $100 \times 10^9/L$  might have the highest risk of CNS relapse. Inadequate CNS-directed therapy for these patients might not only increase the risk for CNS relapse, but also lead to a higher rate of hematologic relapse.<sup>5</sup> As shown in Table 1, CNS relapse or BM relapse were usual findings in control group patients. The final outcome was poor; cure (or five years event free survival) was seen in only 5 out of 30 (16.7%) patients of control group. However, 25 out of 30 (83.3%) patients had either CNS or BM relapse or died. Lazarus et al. reported that despite intensified chemotherapy and craniospinal irradiation or hematopoietic stem cell transplantation with total-body irradiation, those with CNS leukemia at diagnosis had a significantly higher risk for any type of CNS relapse, whether isolated or combined (11.9% vs. 5.6%). These patients also had a poorer survival rate (29% vs. 38%) at 5 years compared with all other patients.<sup>6</sup> The poor

results in the case of primary CNS involvement or first CNS relapse, even in pre-B cell ALL which is common in children, have led to numerous attempts to decrease mortality and morbidity. Attempts included high dose intravenous methotrexate. However, a meta-analysis of 43 randomized trials, showed that high-dose methotrexate reduced the hematologic relapse rate and improved event-free survival, but had only a marginal effect on the control of CNS leukemia.<sup>7</sup> Others preferred dexamethasone to prednisolone,<sup>8</sup> however this was not effective in other studies.<sup>9</sup> In the current prospective randomized case-control study boys with either primary CNS involvement or first CNS relapse had better prognoses if received extended intrathecal chemotherapy in the fourth and fifth year after induction of remission. (Table 2 and Figures 2-3)

## Conclusion

For centers that do not administer liposomal cytarabine (due to economic restrictions or unavailability of the drug), extended IT injections for two years after discontinuation of maintenance chemotherapy is advisable in cases of primary CNS involvement and CNS relapses. However national and international studies that enroll greater numbers of patients are suggested.

## Acknowledgment

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**Table 2.** Impact of extended central nervous system (CNS) prophylaxis for cases of childhood leukemia with CNS involvement or CNS relapse during 1995-2014 at Shiraz University of Medical Sciences.

Outcome Groups (number)	CNS relapse Sex (n)	BM relapse Sex (n)	Death Sex (n)	P-value (boys vs. girls)
A1: CNS involvement (15)	Boys 3	Boys 3	Boys 2	Chi square: 15.63 $P < 0.001$
	Girls 2	Girls 0	Girls 0	
A2: CNS relapse (15)	Boys 5	Boys 4	Boys 1	
	Girls 2	Girls 2	Girls 1	
B1 CNS involvement (20)	Boys 2	Boys 0	Boys 0	Chi square: 10.16 $P < 0.001$
	Girls 0	Girls 0	Girls 0	
B2 CNS relapse (40)	Boys 3	Boys 1	Boys 1	
	Girls 7	Girls 3	Girls 2	
Total (90)	Boys 15/50	Boys 9/50	Boys 4/20	
	Girls 7/40	Girls 3/40	Girls 2/40	

BM: Bone marrow.

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### Conflict of interest

No conflict of interest is declared.

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