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Comparison of CNS Relapse, Survival and Intelligent Quotient in Non-High Risk ALL Children Treated with Intrathecal Methotrexate or Triple Intrathecal Therapy

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Abstract

Background

Compared to intrathecal methotrexate (IT MTX), triple intrathecal therapy (TIT) has shown promising results in decreasing central nervous system (CNS) relapse in children with acute lymphoblastic leukemia (ALL). We aimed to compare these two IT regimens in terms of CNS relapse, survival, and IQ in Iranian non-high risk ALL children.

Materials and Methods

In a two phases clinical trial study, 203 children with non-high risk ALL, aged 1-10 years at diagnosis, who were previously treated with the same systemic protocol but with two different IT regimens, based on IT regimen allocated to IT MTX (n = 109) and TIT (n = 84) groups were studied. In phase 1, isolated CNS relapses (i-CNS) and five-year survival of the two groups was compared, and in phase 2, IQ score of survivors of two groups was measured and compared.

Results

The overall rate of i-CNS relapse was 13.8% and the incidence of i-CNS relapse in contrast to other areas in the IT MTX group, was higher than in the TIT group (17.4% vs. 9.6%; P= 0.03). Most i-CNS relapses were asymptomatic and "early" and there was no significant relation between IT formulation and secondary relapse and mortality rate in patients with i-CNS relapse (P> 0.05). The 5-year survival of TIT group was more than the IT MTX group (80.9% vs.70.6%; P=0.04), but the mean scores of full-scale, verbal, and performance IQ (except cubes) were not significantly different in the two groups.

Conclusion

Based on the results, TIT regimen compared to IT MTX reduced i-CNS relapse and increased 5-year survival in Iranian children with ALL but had no significant differences in total IQ score.

Key Words: Children, Leukemia, Therapeutics, Recurrence, Survival.

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1- INTRODUCTION

Central nervous system relapse is an important prognostic factor in the treatment of childhood leukemia. Before the application of CNS prophylaxis, over 50% of patients with ALL experienced CNS relapse after hematologic remission and thus suffered from more systemic relapses (1). The introduction of CNS prophylaxis in the early 1970s improved the prognosis of ALL and the long-term disease-free survival. The first modality for CNS prophylaxis was combination of 2400 cGy cranial RT (CRT) and intrathecal methotrexate which reduced CNS relapse to less than 10% and improved long-term survival but it was associated with serious long term complications such as neurocognitive impairments and secondary malignancies (1-4). For this reason, in subsequent studies CRT was replaced by risk-adjusted systemic chemotherapy and extended IT therapy for all groups of ALL (except T-ALL) (5-8). Although replacement of CRT by chemotherapy could significantly improve neurocognitive outcomes, compared with general population the frequency of these problems is still high (3, 9).

In most ALL treatment protocols, there are two strategies for intrathecal prophylaxis (IT MTX or TIT) and one of the two is chosen as CNS prophylaxis, depending on treatment protocol and treatment center strategy. Children's Cancer Group (CCG) protocols have used IT MTX as a standard regimen for CNS prophylaxis since 1977 but subsequently some investigators added cytarabine and hydrocortisone to the IT MTX regimen in order to obtain greater efficacy. Matloub et al. revealed, although TIT compared with IT MTX can decrease CNS relapse, this regimen fails to improve event-free survival of children with standard risk ALL (1). Moreover, Salzer et al. also showed TIT compared to IT MTX cannot improve disease-free survival of children with high risk B-ALL (10), so due to these reasons and probabilities of more toxicities, use of this regimen in low risk ALL patients is questionable and the decision of whether to use it needs further studies. In addition, most previous studies compared CRT with chemotherapy only (11, 12) and there are few studies that compare the two IT regimens as CNS prophylaxis. In this study we compared IT MTX with TIT in terms of CNS relapse, survival, and intelligence quotient (IQ) in Iranian non- high risk ALL children with the aim of establishing a local guideline for intrathecal therapy in our patients.

2- MATERIALS AND METHODS

2-1. Study population

In order to achieve the above goal in a clinical trial study of 305 children with ALL, 203 non-high risk children, with aged 1-10 years at diagnosis were recruited in study. The patients were treated with the same systemic protocol but with two different IT regimens (IT MTX or TIT). The eligible patients were assigned based on CNS prophylaxis regimen into IT MTX (n= 109), and TIT (n= 94) groups. IT MTX group were treated with age-adjusted IT MTX (1yr ≤ age < 2yr: 8mg; 2yr ≤ age < 3yr: 10mg; and age ≥3yr: 12mg) and TIT group received TIT as (1yr ≤ age < 2yr: MTX 10mg, cytarabine 20mg, and hydrocortisone 10 mg; 2yr ≤ age < 3yr: MTX 12 mg , cytarabine 25 mg, and hydrocortisone 12 mg; age ≥3yrs: MTX 15mg, cytarabine 30 mg, and hydrocortisone 15 mg).

2-2. Study design

This study was performed in two phases:

Phase.1: Baseline characteristics and laboratory findings, including the results of cell blood count (CBC), Bone marrow (BM) aspiration at diagnosis (morphology, immunophenotype, and cytogenetic), cerebrospinal fluid (CSF) analysis, duration and details of treatment, and

modality of CNS prophylaxis were extracted from patient files. Isolated CNS relapse was assessed based on the presence of lymphoblast in CSF centrifuge preparation associated with at least 5 WBCs/mm3 of CSF without relapse in other sites (1). Early and late CNS relapses were defined as those occurring respectively < 18 months or ≥18 months after the first complete remission (CR1) (13). Isolated BM relapse was also diagnosed based on the presence of over 25% lymphoblast in BM reports and isolated testicular relapse was determined based on the pathology report of blasts in biopsy specimen of testis in suspected patients (1). Five-year survival was measured as the percentage of patients who were alive for five years after the beginning of treatment for ALL (14).

Phase.2: In this stage survivors of each group who had no overt neurological complications or recurrence in other sites and were in the age range 6-16 years-old, were tested for IQ. The sample size for each group was statistically calculated to be 28 children using the following equation:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (SD_1^2 + SD_2^2)}{d^2} = \frac{(1.96 + 0.84)^2 (10.3^2 + 9^2)}{7.2^2} = 28$$

Thirty eligible subjects were in IT MTX group and 32 eligible survivors were in TIT group. IQ test was done voluntarily by an expert psychologist in hospital at no cost to the patient. Full-Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) scores of subjects of each group were measured and compared.

2-3. Inclusion and exclusion criteria

Inclusion criteria: The diagnosis of ALL was made by cytomorphological and immunophenotyping examination of bone marrow (13) at the two pathology institutions under Isfahan University of Medical Sciences supervision, by expert pathologist in each lab. The patients with the following criteria were selected to be included in this study:

- Age between 1-10 years at diagnosis,
- A confirmed diagnosis of ALL,
- White blood cell (WBC) count below 50×10^9/L at the time of diagnosis,
- Absence of high-risk cytogenetic abnormalities including t(4;11), t(1;19), t(9;22), MLL gene rearrangements at chromosome band 11q23, and hypodiploidy (≤45 chromosome) (13), and
- Cessation of treatment at least one year before the study.

Exclusion criteria: Exclusion criteria were also as follows:

- Having a history of developmental delay, L3 morphology, T-cell phenotype,
- CNS or testicular involvement at the time of diagnosis,
- Induction failure, and
- History of CRT.

2-4. Measuring tools

Survivors underwent IQ test using the revised Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) that is standard for Iranian population (15, 16). The WISC-IV is a general test of intelligence that is designed for children between the ages of 6 and 16 year-old and contains 10 core tests and 5 additional tests. The revised test includes verbal subscales (information, similarities, arithmetic, vocabulary and comprehension), and performance subscales (picture completion, picture arrangement, object assembly, cubes and coding). The Full Scale IQ (FSIQ) is composed of the above 10 core subtests and has a standardized mean and SD of 100 and 15, respectively. The split-half reliability coefficients of all subscales were 79-96% and the validity of them was

approved by expert opinions (15, 17). Descriptive statistics parameters of raw scores of sub-scales of survivors were calculated and raw scores were converted to standard scores using non-linear transformation using Z- table. The standard scores of each subscale were converted linearly to a scaled score with an average of 10 and standard deviation of 3.

2-5. Ethical consideration

This randomized clinical trial study (ID-code: TCTR20190702002), was approved by the Research Deputy and Ethics Committee of School of Medicine, Isfahan University of Medical Sciences (ID-code: 394915 and IR.MUI.REC.1394.3.915, respectively), and a written informed consent was obtained from parents who allowed their children to participate in the study.

2-6. Data Analyses

SPSS software (version 22.0) was used for numerical data analysis of group comparison. For continuous variables mean and standard deviation (SD) were estimated and for numerical data, we conducted an independent *t-test* to compare the difference between the means. For categorical data, we used Chi-square test and Fisher's exact test for comparison. For all statistical procedures, p-value less than 0.05 was considered to be significant.

3- RESULTS

3-1. Patient and leukemia characteristics

From the 305 evaluated patients, 203 children were eligible to participate in this study. All eligible patients were treated with the same systemic protocol (modified BFM76/79), but 109 patients received IT MTX and 94 patients received TIT as CNS prophylaxis. Patient characteristics and laboratory findings are summarized in **Table.1**. As seen, the patients had no significant differences at baseline.

Table-1: Patients characteristics and laboratory findings in Non-high risk ALL children treated with IT MTX or triple IT.

Variables	IT MTX Group(n=109)	Triple IT Group(n=94)	P-value
Age at diagnosis (year) Mean ± SD	5.5±2.9	5.6±3.3	0.86
Gender Female Male	 50 (52.8%) 59 (54.1%)	 44 (46.8%) 50 (53.2%)	0.89
Leukocyte count (mm^3) ≤ 4000 4000-20,000 20,000-50.000	 20 (18%) 47 (43%) 42 (39%)	 23 (25%) 49 (52%) 22 (23 %)	0.30
Hemoglobin(g/dl) ≤ 7.0 7.0-11.0 > 11.0	 32 (30%) 70 (64%) 7 (6%)	 30 (32%) 61 (65%) 3 (3%)	0.49
Platelet count (mm^3) ≤ 20,000 20,000-100,000 > 100,000	 31(28%) 51(47%) 27(25%)	 23 (25%) 49 (52%) 22 (23%)	0.97
Morphology of ALL L1 L2	 35 (32%) 74 (68%)	 25 (27%) 67 (73%)	0.71

Immunophenotype of ALL Pro-B, $CD10^-$ Precursor- B, $CD10^+$ Pre- B cell	 12 (11%) 25 (23%) 72 (66%)	 9 (10%) 23 (24%) 62 (66%)	0.11
Chromosomal abnormalities Tel/AML fusion Normal diploid Hyper diploid	 9 (8%) 98 (90%) 2 (2%)	 7 (8%) 87 (92%) –	0.28

ALL: Acute lymphoblastic leukemia; IT: Intrathecal; IT MTX: Intrathecal methotrexate; SD: Standard deviation

3-2. Isolated CNS relapses and their outcome

In general, 28 patients had isolated relapse and the overall rate of CNS relapse was 13.8%. CNS was the most common site of relapse in all patients and also in the IT MTX group, but in the TIT group BM was the first, followed by CNS. The incidence of i-CNS relapse was more in the IT MTX group than in the TIT group (17.4% vs. 9.6%; P= 0.03), but the incidence of relapse in other sites was not significantly different between the two groups (**Table.2**). The characteristics, clinical presentation, and outcome of patients with i-CNS relapse are shown in **Table.3**. The findings of the **Table.3** revealed that majority of isolated CNS relapses were identified after IT administration by CSF analysis in asymptomatic patients and most of them occurred as "early relapse" in two groups. Secondary BM relapses were seen in 57.9% of IT MTX group and 44.4% of TIT group with i-CNS relapse but there was no significant relation between IT formulation and secondary relapse site (P> 0.05). The IT MTX and TIT groups had no significant differences in terms of mortality rate in i-CNS relapsed cases (68.4% vs. 67.6%; P = 0.40).

3-3. Patient outcomes

The findings showed that the overall five-year survival rate for all 203 eligible patients was 74.9% and the TIT group had a significantly higher survival rate compared to the IT MTX group (80.9% vs.70.6%; P = 0.04; **Table.4**).

Table-2: The incidence of isolated relapses in Non-high risk ALL children treated with IT MTX or triple IT.

Variables	IT MTX Group (n=109)		TIT Group (n=94)		P-value
Relapse site	Number	%	Number	%	
CNS	19	17.4	9	9.60	0.03
BM	11	10.1	11	11.7	0.44
Testis	0	0.00	1	1.10	0.56
Lung	1	0.90	0	0.00	0.54
Total	31	28.4	21	22.4	0.42

IT MTX: Intrathecal methotrexate; TIT: Triple intrathecal; CNS: Central nervous system; BM: Bone marrow.

Table-3: The characteristics, clinical presentation, and outcome of patients with i-CNS relapse.

Variables	IT MTX Group, (n=19)	Triple IT Group, (n=9)	P-value
Age (year) Mean ± SD Range	 5.6±3.3 2-15	 5.8±3.7 2-13	0.89
Gender Male Female	 9 (47.4%) 10 (52.6%)	 7 (77.8%) 2 (22.2%)	0.07
Symptomatic	5 (26.3%)	3 (33.3%)	0.52
Asymptomatic	14 (73.7%)	6 (66.7%)	
Early relapse	14 (73.7%)	6 (66.7%)	0.52
Late relapse	5 (26.3%)	3 (33.3%)	
BM relapse	11 (57.9%)	4 (44.4%)	0.16
Testis relapse	2 (10.5%)	0 (00.0%)	0.18
Death	13 (68.4%)	6 (67.6%)	0.40

i-CNS: Isolated central nervous system; IT MTX: Intrathecal methotrexate; IT: Intrathecal; SD: Standard deviation.

Table-4: Five-year survival in IT MTX and triple IT groups.

Variables	IT MTX Group (n=109)		Triple IT Group (n=94)		P-value
	Number	%	Number	%	
Surviving	77	70.6	76	80.9	0.04
Dead	32	29.4	18	19.1	

IT MTX: Intrathecal methotrexate; IT: Intrathecal.

3-4. IQ scores in the survivors of IT MTX and TIT Groups

Overall, intelligent quotient (IQ) tests were done in 30 survivors of the IT MTX group and 32 survivors of the TIT group. As seen in **Table.5**, these patients had no significant differences in terms of demographic characteristics (P>0.05). The findings revealed that the mean scores of FSIQ, VIQ, and PIQ subtests were not significantly different in the survivors of the two groups as well (**Tables.6**), but the mean score of cubes (belonging to the PIQ subset) was significantly lower in the IT MTX group than in the TIT group (P= 0.02; **Table.6**). Consort diagram of study is shown in **Figure.1**.

Table-5: Baseline characteristics and Intelligence quotient scores in survivors of IT MTX and TIT groups.

Variables	IT MTX Group, (n=30)	TIT Group, (n=32)	P-value
Age (year) Mean± SD Range	 10.3± 2.6 7-15	 10.1± 2.8 6-16	0.80
Gender Female Male	 17 (56.7%) 13 (43.3%)	 17 (53.1%) 15 (46.9%)	0.87
FSIQ Mean ± SD	 88.7± 10.8	 93.6± 13.8	0.28
VIQ Mean ± SD	 95.6± 12.8	 96.1± 14.3	0.92
PIQ Mean ± SD	 84.5± 13.5	 90.9± 14.3	0.21

IT MTX: Intrathecal methotrexate; TIT: Triple intrathecal; SD: Standard deviation; FSIQ: Full scale intelligence quotient; VIQ: Verbal IQ; PIQ: Performance IQ.

Table-6: Comparison of verbal and performance IQ subtests scores in IT MTX and triple IT groups.

Subtest	IT MTX Group		Triple IT Group		P- value
Verbal IQ	Mean	SD	Mean	SD	
Information	8.75	2.27	8.53	3.16	0.83
Similarities	8.13	2.94	8.60	2.95	0.66
Mathematic	10.56	2.85	9.27	3.26	0.25
Vocabulary	9.06	3.23	10.80	4.54	0.23
Comprehension	10.31	2.57	10.53	2.80	0.82
Performance IQ					
Picture completion	8.56	2.85	8.53	2.85	0.98
Picture arrangement	5.81	2.14	7.07	2.74	0.16
Object assembly	8.13	2.28	9.07	3.43	0.44
Cubes	8.06	2.99	10.60	2.44	0.02
Coding test	8.44	2.56	7.93	3.37	0.64

IQ: intelligence quotient; IT MTX: Intrathecal methotrexate; IT: intrathecal.

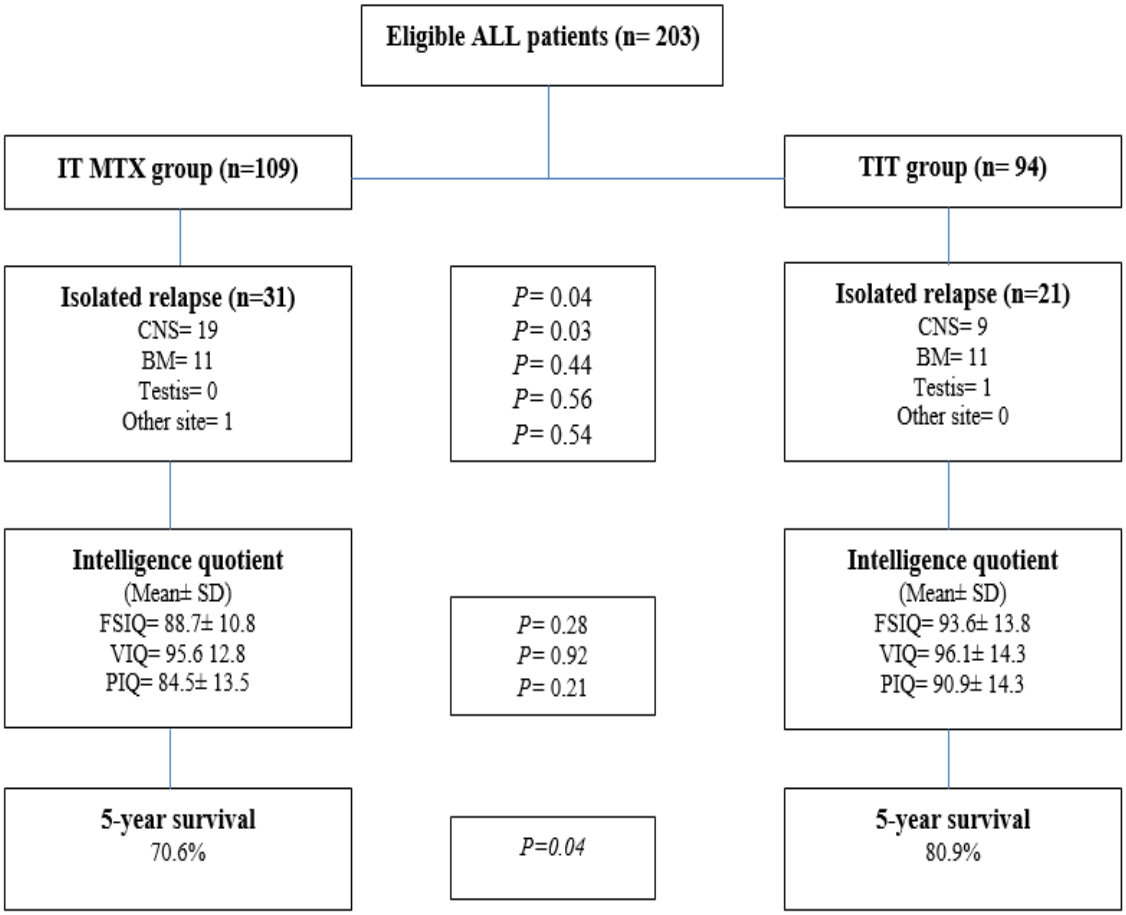

Fig.1: Consort diagram showing study flow, isolated relapse, intelligence quotient scores and 5-year survival in study patients.

4- DISCUSSION

In this study we compared two regimens of IT MTX with TIT in terms of CNS relapse, survival, and intelligence quotient (IQ) in Iranian non-high risk ALL children with the aim of establishing a local guideline for intrathtecal therapy in our patients. The findings of the present study indicated that 13.8% of all investigated patients had isolated relapse, and the CNS was the most common site of relapse in all patients. Overall, 20–40% of relapses of ALL occur in the CNS (10, 14), and the incidence of isolated CNS relapse is reported 5-10%. Our findings showed a higher incidence of i- CNS relapse as compared to the previous studies (1, 18, 19). The reason for such differences is not clear.

However, in our research some of the factors associated with the possibility of CNS relapse including age less than 1 year and more than 10 years, T-cell immunophenotype, hyperleukocytosis, high-risk genetic abnormalities, and CNS disease at diagnosis (1, 18, 20) were controlled using exclusion criteria, and omitting the ineligible subjects, but the role of other predictive factors of CNS relapse such as traumatic tap, nodal enlargement, hepatosplenomegaly, mediastinal mass and genetic differences in the metabolism of anti-cancer drugs (1, 20) were not controlled in this research. Therefore, a larger comprehensive study is recommended in this regard.

The other finding of this study was the higher incidence of i-CNS relapse in the IT MTX group compared with the TIT group. This finding was in line with the findings of Matloub et al.'s study that showed a lower six-year cumulative incidence of i-CNS relapse in the TIT group than in the IT MTX group (1). These results, regardless of the treatment complications can strengthen the notion that TIT is more effective than IT MTX for CNS-directed therapy of children with non- high-risk ALL. The finding of the present study also revealed that the most common recurrence site for the IT MTX group was the central nervous system and for the TIT group, however, bone marrow was the first recurrence site and the CNS was the second site. This finding was consistent with the findings of Matloub et al.'s study. It seems that the synergic and prophylactic effects of MTX plus cytarabine are responsible for lower incidence of CNS relapse in the TIT group with respect to the IT MTX group, but the potential effects of TIT which can shift the site of relapse from CNS to BM or other sites should be taken into consideration (1).

Most relapses of ALL occur during treatment or during the first years of treatment cessation (1, 20), and more CNS relapses are asymptomatic and they can occur as isolated or combined. Some researchers believe that "CNS relapse does not, in fact, occur in isolation and is largely a local manifestation of systemic failure" (1). In the present study more CNS relapses were also asymptomatic and they happened as "early relapse" and there was no significant relation between IT regimen and the time of relapse. This was also true about secondary relapse sites and mortality rate of children with i-CNS relapse.

Relapse attacks are one of the most important factors affecting the survival rate of children with leukemia. Both the incidence of relapse and the frequency of it are involved (21). In recent years with advances occurred in treatment protocols, the overall survival rate of children with ALL has increased 80% to90% (3, 10, 22), but 5-year survival rate of patients with CNS relapse according to the time of relapse dropped 43% to 68% (20). Karimi et al. reported a 5-year survival rate of 72% for ALL children in Iran (23), and our results are consistent with the findings of this study. This study also compared the TIT and IT MTX groups in terms of IQ scores. The findings revealed that the

mean scores of FSIQ, VIQ, and PIQ subtests were not significantly different in the survivors of the two groups, but the mean score of cubes (a subset of the PIQ) was lower in children treated with IT MTX than the TIT group. Kadan-Lottick et al. also reported similar results except for a slight worsening of the processing speed index in the survivors of IT MTX group (4). Various neurocognitive function deficits were reported in survivors of childhood leukemia who do not receive CRT (11, 24, 25), and exposure to IT medication may be a possible cause (4).

Some researchers demonstrate that ALL survivors who received chemotherapy only had lower intelligent quotient comparing to control group (24, 26, 27). Lyer et al. in a meta-analysis study showed significant IQ deficits of 6 to 8 points compared with healthy controls (28), and Halsey et al. who measured IQ scores in patient before and after leukemia treatment showed a significant reduction of between 3.6 and 7.3 points in IQ scores of ALL patient comparing with control groups (9). Although our results showed the formulation of IT therapy had no significant effects on general IQ, more studies are needed to evaluate the subtests accuracy.

4-1. Study Limitations

This study had several limitations including: 1- a part of data was collected from previously treated patients and we could not control all confounding variables, 2- this study is conducted on the subjects from two local hospitals in Isfahan province and caution should be taken when generalizing the findings to statistical population, 3- we had no healthy control group for IQ test.

5- CONCLUSION

Based on the findings of this study TIT regimen compared to IT MTX reduced i-CNS relapse and increased 5-year survival in children with non-high risk ALL but had no significant adverse effect on total IQ. Therefore, we can recommend TIT as CNS prophylaxis regimens in our patients.

6- CONFLICT OF INTEREST: None.

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8- REFERENCES

1. Matloub Y, Lindemulder S, Gaynon PS, Sather H, La M, Broxson E, et al. Inthrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with inthrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. Blood 2006; 108(4): 1165–73.

2. Pui CH. Acute lymphoblastic leukemia: Introduction. Semin Hematol 2009; 46(1):1-2.

3. Liu W, Cheung YT, Conklin HM, Jacola LM, Srivastava D, Nolan VG, et al. Evolution of neurocognitive function in long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. Cancer Surviv 2018; 12(3): 398-406.

4. Kadan-Lottick NS, Brouwers P, Breiger D, Kaleita T, Dziura J, Northrup V, et al. Comparison of Neurocognitive Functioning in Children Previously Randomly Assigned to Intrathecal Methotrexate Compared With Triple Intrathecal Therapy for the Treatment of Childhood Acute Lymphoblastic. Leukemia 2009; 27(35): 5986–92.

5. Liu H-C, Yeh T-C, Hou J-Y, Chen K-H, Huang T-H, Chang C-Y, et al. Triple intrathecal therapy alone with omission of cranial radiation in children with acute lymphoblastic leukemia. J Clin Oncol 2014; 32(17):1825-29.

6. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J M 2009; 360(26): 2730-41.

7. Sison EA, Silverman LB. CNS prophylaxis in pediatric acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2014; 2014(1):198-201.

8. Vora A, Andreano A, Pui CH, Hunger SP, Schrappe M, Moericke A, et al. Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy. J of Clin Oncol 2016; 34(9): 919-26.

9. Halsey C, Buck G, Richards S, Vargh-khadem F, Hill F, Gibson B. The impact of therapy for childhood acute lymphoblastic leukaemia on intelligence quotients; results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI. J Hematol Oncol 2011; 4:42.

10. Salzer WL, Burke MJ, Devidas M, Gore L, Hilden JM. Triple Intrathecal Therapy (Methotrexate/Hydrocortisone/Cytarabine) Does Not Improve Disease-Free Survival versus Intrathecal Methotrexate Alone in Children with High Risk B-Lymphoblastic Leukemia: Results of Children's Oncology Group Study AALL113. Blood 2018 132 no. Suppl 1 35 doi: https://doi.org/10.1182/blood-2018-99-116180.

11. Kim SJ, Park MH, Lee JW, Chang NG, Cho B, Lee IG, et al. Neurocognitive Outcome in Survivors of Childhood Acute Lymphoblastic Leukemia: Experience at a Tertiary Care Hospital in Korea. J Korean Med Sci 2015; 30: 463-69.

12. Zając-Spychała O, Pawlak M, Karmelita-Katulska K, Pilarczyk J, Jończyk-Potoczna K, Przepióra A, et al. Anti-leukemic treatment-induced neurotoxicity in long-term survivors of childhood acute lymphoblastic leukemia: impact of reduced central nervous system radiotherapy and intermediate- to high-dose methotrexate. Leuk Lymphoma 2018; 59(10): 2342-51.

13. Carroll WL, Bhatla T. Acute lymphoblastic leukemia. In: Lanzkowsky P, Lipton JM, Fish JD. Lanzkowsky's Mannual of pediatric hematology and oncology. 6th ed. USA: Academic Press; 2016: 367-89.

14. Survival rate. In: NCI Dictionary of cancer terms. Revised April 5, 2018. [Cited 2018 Jul 1]. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survival-rate.

15. Wechsler D. The Wechsler intelligence scale for children. 2003 4th ed. San Antonia, TX: Psychological Corp.

16. Abedi MR, Sadeghi A, Rabiei M. Standardization of the Wechsler children's IQ test (Fourth Edition) in Chaharmahal and Bakhtiari Province. Quarterly Personality and Individual Differences 2013; 2(3): 138-58.

17. Sadeghi A, Rabiee M, Abedi MR. Validation and reliability of the Wechsler Intelligence Scale for Children-IV. Developmental Psychology: Journal of Iranian Psychologists 2011; 7(28): 377-86.

18. Cancela CSP, Murao M, Viana MB, Oliveira BM. Incidence and risk factors for central nervous system relapse in children and adolescents with acute lymphoblastic leukemia. Rev Bras Hematol Hemoter 2012; 34(6): 436–41.

19. Arora B, Kurkure PA. Relapsed testicular leukemia: Local insights in to a vanishing disease. Indian journal of cancer 2010; 47(2):93-4.

20. Sang-Hyun Sung, In-Seok Jang. Isolated Central Nervous System Relapse of Acute Lymphoblastic Leukemia. Brain Tumor Res Treat 2014; 2(2): 114–18.

21. Almasi-Hashiani A, Zareifar S, Karimi M, Khedmati E, Mohammadbeigi A. Survival rate of childhood leukemia in shiraz, southern Iran. Iran J Pediatr 2013; 23(1): 53-8.

22. Parvareh M, Khanjani N, Farahmandinia Z, Nouri B. The Survival of Childhood Leukemia and its related factors in Kerman, Iran. Iran J Health Sci. 2015; 3(4): 24-32.

23. Karimi M, Yarmohammadi H, Sabri M.R. An analysis of prognostic factors and the five-year survival rate in childhood acute lymphoblastic leukemia. Med Sci Monit 2002; 8(12): 792-96.

24. Jacola L, Ederstein K, Liu W, Pui CH, Hayashi R, Kadan-Lottick N, et al. Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. Lancet Psychiatry 2016; 3(10): 965-72.

25. Chiou SS, Lin PC, Liao YM , Yang P. A cross-sectional follow-up study of physical morbidities, neurocognitive function, and attention problems in posttreatment childhood acute lymphoblastic leukemia survivors. Kaohsiung J Med Sci 2019; 1–6.

26. Lofstad E, Reinfjell T, Hestad K, Diseth T. Cognitive outcome in children and adolescents treated for acute lymphoblastic leukaemia with chemotherapy only. Acta Paediatr. 2009; 98(1): 180–86.

27. Iyer N, Balsamo N, Bracken M, Kadan-Lottick N. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. BLOOD 2015; 126(3): 346-53.

28. Laningham FH, Kun LE, Reddick WE, Ogg RJ, Morris EB, Pui CH. Childhood central nervous system leukemia: Historical perspectives, current therapy, and acute neurological sequelae. Neuroradiology 2007; 49(11): 873-88.