Original Article

The Effects of Prophylactic Treatment of the Central Nervous System on the Intellectual Functioning Of Children with Acute Lymphocytic Leukemia

Hashemi A[1] MD, Ghilian R[2] MD, Mohammadian R[3] BSc, Nodehi M[3] BSc

1-Department of Pediatrics, Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran
2- Internal Medicine. Hematology oncology and Genetics Research Center Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran
3- Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

Received: 15 March 2011
Accepted: 21 July 2011

Abstract
Objective
The great majority of patients with childhood leukemia become long-term survivors. They treated with chemotherapy and prophylactic central nervous system (CNS) irradiation. The aim of this cross-sectional study was to evaluate effect of the long-term toxicity in ALL survivors, and possible effects of this treatment on their intellectual in compare with their sibling.
Materials and Methods
In this case-control study 40 children, 20 ALL patients and 20 their sibling, were evaluated. This study chose 20ALL patients, which they sibs were 1 or 2 years younger or older and same sex. Patients were diagnosed in Shahid Saduoghi hospital and treated with single chemotherapy (systemic and intrathecal) and radiation therapy (1800 rad).
Variables such as age, treatment outcome, genesis and the effect of prophylactic treatment of the CNS on the intellectual function of ALL patients were studied and compare with their healthy sibling by Wechsler intelligent test.
Results
Age range was between 6 to12 years old. The mean verbal IQ score for patients was 113.25+/-13.35 and in their sibling was 113.25+/-14.74. (p=1), therefore the differences was not significant.
Conclusion
The mean verbal IQ score for patients that received low dose radiotherapy was in the average range. These preliminary findings provide direction for future studies to help identify high-risk patients.

Keyword
Central nervous system, Intellectual quotient, lymphocytic leukemia

Corresponding Author:
Rozita Gilian, – Internal Medicine. Hematology oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd- Iran.

[Downloaded from ijpho.ssu.ac.ir on 2024-10-12]

Intoduction

By using more intensive treatment protocols, the prognosis of acute lymphoblastic leukemia (ALL) in childhood has dramatically improved over the past 30 years, achieving cure rates of at least 70% (1). With the rising number of long-term survivors, it has become evident that more intensive therapies, especially more efficacious CNS prophylaxis, can induce late toxicities, particularly neuropsychological (cognitive) disabilities (2).

Numerous studies have addressed the issue of cognitive functions after treatment of leukemia in children, most often through intelligence quotient (IQ) measurement (3-6).

In the 1970s and early 1980s, CNS treatment consisted of cranial irradiation and intrathecal chemotherapy. Reports of intellectual dysfunction after cranial irradiation led to the replacement of irradiation by intrathecal and high-dose CNS-directed chemotherapy in most current protocols (7, 8).

The few prospective studies revealed to indicate that the development of cognitive disabilities increases over time, both after receiving chemotherapy alone and chemo-radiotherapy as CNS prophylaxis, but that there is no clear-cut difference between those children having received prophylactic CNS irradiation and those not having received it (9,10).The different results reported in other studies (11) may be due to the methodological difficulties and pitfalls encountered when assessing neuropsychological disabilities in long-term survivors (12).

In the present study, intelligence quotient (IQ) of patients after prophilactic treatment and population-based matched controls were evaluated (their sibiling).

Materials and Methods

Between 2004-2010, the 20 ALL patients that treated in Shahid Sadughi hospital in Yazd evaluted for effects of CNS prophylactic treatment on verbal IQ. The eligibility requirements for entry onto their study : 1) diagnosis of ALL based on the presence of greater than 25% blasts in the bone marrow .2) age between 6-12 years at the time of diagnosis 3) treated on protocol CCG-101 without CNS and BMD relapse(4). Received prophylactic treatment. All the patients presented in this report received vincristin , cytosar , Etoposide , L.asparginase , Adriamysin , cortico Estroeid and radiation with 1800 rad and intrathecal metotrexat each 3 to 6.

This study was case control. 40 cases evaluated Patients and a sample of their helthy sibling as a comparison group. So we has two groups : healthy siblings and patients. No significant differences were observed between patients and siblings with respect to age, sex, type of CNS treatment.

At the time of testing, case ranged in age was 6-12years (median 8.72+/- 2.36) that median in patients was 8.55+/-2.25and in their sibling was 8.9+/-2.51 (p=0.646).

Two groups were simple in sex. In both 11 male (55%) and 9 female (45%) had been.

Wechsler intelligent Scale for children-Revised (WISC-R) was used for testing the effect of prophylactic treatment of central nervous system on the intellectual functioning.

The Mann-Whitney U test was used for the statistical analysis of IQ data. A p-value of <0.05 was considered to be statistically significant.

Results

The mean verbal IQ for the group was 113.25, with one standard error of the mean (SEM) being 13.88 and with scores ranging from 90 to 138.the mean verbal IQ score for patients was 113.25+/-13.35 and in their sibling was 113.25+/-14.74. (p=1)Thus overall IQ of all patients were equal with the sibling.

Analysis was performed to identify those patients' characteristics which may be correlated with IQ score. Included in the analysis were the variables of sex and age.

[Downloaded from ijpho.ssu.ac.ir on 2024-10-12]

The mean verbal IQ score for females was 113.22+/-10.03 compared to 113.27+/-16.63 for males. (p=0.991) that was equal for both group.
In both groups 8 cases (40%) were fewer 7 years old and 12 cases (60%) were more than 7 years old. Pair wise comparison between the age groups did not demonstrate any statistically significant differences because the mean verbal IQ score for cases who were less than 7 years of age was 119.56+/-92 compared to 109.04+/-15.01 for who were more than 7 years of age. (p=0.009)

Discussion

Improvement in the survival of children with ALL has been dramatic over the past 30 years. Therefore, the question of long-term performance in the biologically cured patients is becoming always more relevant.
The routine use of central nervous system (CNS) prophylaxis therapy, including whole brain radiation, intratecal chemotherapy , and high-dose systemic chemotherapy has contributed to the progress in long-term disease-free survival from acute lymphoblastic leukemia (ALL) in children subsequently may experience declines in intellectual, academic and neuropsychological skills , often called CNS late effects (Fletcher and Copeland, 1988)
In this study did not find significantly difference between patients and their sibling controls. Our results were encouraging: all of ALL long-term survivors' presented no or only minimal late toxicity.
The similar studies were defined Howard and coworkers studied on 24 children at 2004. The mean full scale IQ was 98.6 for the patients and 112.5 for sibling controls In this study did not find significantly difference between patients and their sibling controls.
In study that performed by Rabinson and coworkers on 50 long-term servivors between 1972-1974 , the mean full scale IQ score for the group was 95 with mean verbal IQ of 94.4 and mean performance IQ of 96.6. Factors which were found to be closely associated with a lower IQ score included female sex, longer duration of chemotherapy and younger age at the time of radiation (13).
In the study by Von der weid N in Swiss, the mean global, verbal and non-verbal IQs (103, 105 and 101 respectively) of the ALL survivors as a group were comparable with those found in the general population. The mean IQs observed in ALL survivors were not significantly different from those theoretically expected in a random population of healthy Swiss children and adolescents (mean IQ of 100, standard deviation of 15, percentage of learning disabilities (i.e. g IQ <85) (16%). Neither gender (although females scored slightly poorer than males in vIQ) nor duration of follow-up showed the same statistically significant impact (2).
A recently published study from the German BFM group reported no striking cognitive deficiencies in former ALL children treated with 12 Gy prophylactic cranial irradiation (14).
In the study by Haupt et al 92.4% of leukemia survivors had completed high school, which did not differ from their sibling controls (15).
In the other hand in study that performed by Harila AH and coworkers in Finland, A decline of school marks was observed in leukemia patients treated with chemotherapy and cranial irradiation. The decline was most pronounced in the young females diagnosed before school age and in the marks for foreign language. The most significant limitation of this study is the lack of treatment data, which hampered the analysis of the effects of different treatment modalities or doses. Female leukemia patients were found to have a greater decline in school marks in several school subjects (16).
Mitby et al also found female leukemia survivors to show a greater difference compared with controls in the utilization of special education services (17). Haupt et al found a greater

[Downloaded from ijpho.ssu.ac.ir on 2024-10-12]

difference in school marks among females, but only in children diagnosed with leukemia before school age and exposed to 24 Gy of cranial irradiation (15).
Hertzberg H,et al Corresponding to the different kinds of CNS prophylaxis, the patient sample was divided: group A (n = 39) receiving intrathecal methotrexate (ITMTX) and systemical medium-high-dose methotrexate (SMHDMTX), group B (n = 41) cranial irradiated (in mean 16.8 Gy) and administering ITMTX and SMHDMTX, group C (n = 38) irradiated (in mean 17.1 Gy) and getting ITMTX. These findings were compared with the neuropsychological test results. Abnormal MRI or CCI scans were found in 61/118 patients (51.7%). Fifteen belonged to group A (38.5%), 23 to B (56.1%) and 23 to C (60.5%). Patients with definite CNS changes show reduced neuropsychological test results (18).
In one large study, Hill et al compared young adults treated as children who had been randomly assigned to either intravenous (IV) and intrathecal (IT) methotrexate (MTX; IV-MTX plus IT-MTX) or to CRT (24 Gy) plus IT-MTX. Those patients treated with CRT exhibited a higher prevalence of psychiatric and academic problems as adults (19). Rowland et al similarly demonstrated poorer neuropsychological outcomes in children randomly assigned to 24 Gy CRT or chemotherapy only (20).
All of this differenses significantly can be correlated with higher CI dose (25-32 Gy compared to 18-20 Gy) and younger age at diagnosis (<4.0 years compared to>or = 4.0 years).

In this study we did not find significantly difference between patient and their sibling controls .these data show that medicinal protocol does not have undesirable effect on intellectual functioning of children with ALL.

Acknowledgment
The authors would like to thank also pediatric hematology and oncology group staff for their highly competent and friendly advices and support in the neuropsychological investigations.

References
1. Pui CH. Childhood leukemias. N Engl J Med 1995;332:1618–30.
2. von der Weid . Late effects in long-term survivors of ALL in childhood: experiences from the SPOG late effects study. Swiss Med Wkly. 2001;131(13-14):180-5.
3.Williams JM, Davis KS: Central nervous system prophylactic treatment for childhood leukemia: Neuropsychological outcome studies. Cancer Treat Rev 1986;13:113-127.
4. Cousens P, Waters B, Said J, et al: Cognitive effects of cranial irradiation in leukaemia: A survey and meta-analysis. J Child Psychol Psychiatry 29:839-852, 1988.
5. Cousens P, Ungerer JA, Crawford JA, et al: Cognitive effects of childhood leukemia therapy: A case for four specific deficits. J Pediatr Psychol 1991;16:475-488.
6. Eiser C: Learning difficulties in children treated for leukemia, in Eiser C: Children With Cancer: The Quality of Life. Mahwah, NJ, Lawrence Erlbaum Associates, 2004, pp 98-121 .
7. Pui CH, Campana D, Evans WE: Childhood acute lymphoblastic leukaemia: Current status and future perspectives. Lancet Oncol 2001;2:597-607.
8. Gustafsson G, Schmiegelow K, Forestier E, et al: Improving outcome through two decades in childhood ALL in the Nordic countries: The impact of high-dose methotrexate in the reduction of CNS irradiation—Nordic Society of Pediatric Haematology and Oncology (NOPHO). Leukemia 2000;14:2267-2275.
9. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy or no cranial irradiation. J Clin Oncol 1991;9:1348–56.
10. Ochs J, Mulhern R, Fairclough D, Parvey L, Whitaker J, Ch'ien L, et al. Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: A prospective study. J Clin Oncol 1991;9:145–51.
11. Brown RT, Madan-Swain A, Pais R, Lambert RG, Sexson S, Ragab A. Chemotherapy for acute lymphocytic leukemia: Cognitive and academic sequelae. J Pediatr 1992;121:885–9.

[Downloaded from ijpho.ssu.ac.ir on 2024-10-12]

12. Mulhern RK, Hancock JR, Fairclough D. Methodological issues in studies of neuropsychological function after treatment for acute lymphoblastic leukemia. In: Green DM, d'Angio GJ, editors. Late effects of treatment for childhood cancer. NewYork: Wiley-Liss; 1992. 31–39.
13. Robison LL, Nesbit ME Jr, Sather HN, Meadows AT, Ortega JA, Hammond GD. Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol. 1984;6(2):115-21.
14. Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W, et al. Improved outcome in childhood acute lymphoblastic leukemia despite of reduced use of anthracyclines and cranial radiotherapy: Results of trial ALL-BFM 90. Blood 2000; 95:3310–22.
15. Silverman LB, Gelber RD, Dalton VK, et al: Improved outcome for children with acute lymphoblastic leukemia: Results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97 : 1211 -1218.
16. Harila-Saari AH, Lähteenmäki PM, Pukkala E, Kyyrönen P, Lanning M, Sankila R. Scholastic achievements of childhood leukemia patients: a nationwide, register-based study. J Clin Oncol. 2007 Aug 10;25(23):3518-24.
17. Mitby PA, Robison LL, Whitton JA, et al: Utilization of special education services and educational attainment among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Cancer 2003;97:1115-1126.
18. Waber DP, Turek J, Catania L, Stevenson K, Robaey P, Romero I, Adams H, Alyman C, Jandet-Brunet C, Neuberg DS, Sallan SE, Silverman LB. Neuropsychological outcomes from a randomized trial of triple intrathecal chemotherapy compared with 18 Gy cranial radiation as CNS treatment in acute lymphoblastic leukemia: findings from Dana-Farber Cancer Institute ALL Consortium Protocol 95-01. J Clin Oncol. 2007;25(31):4914-21.
19. Hill JM, Kornblith AB, Jones D, et al: A comparative study of the long term psychosocial functioning of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate with or without cranial radiation. Cancer 1998;82:208-218.
20. Rowland JH, Glidewell OJ, Sibley RF, et al: Effects of different forms of central nervous system prophylaxis on neuropsychologic function in childhood leukemia. J Clin Oncol 1984;2:1327-1335.

[Downloaded from ijpho.ssu.ac.ir on 2024-10-12]