Original Article

Central nervous system relapse prophylaxis in acute lymphoblastic leukemia (ALL) intrathecal chemotherapy with and without cranial irradiation

Ahmad Tamaddoni (MD)[1]
Hassan Mahmodi Nesheli (MD) [1]
Mohammad Kazem Bakhshandeh Bali (MD)[2*]

Abstract

Background: *Central Nervous System (CNS) relapse in acute lymphoblastic leukemia was significantly decreased due to the use of new chemotherapyeutic agents, Intrathecal chemotherapy and cranial irradiation. The purpose of this study was to compare the effectiveness of intrathecal (IT) CNS chemotherapy alone versus combination of IT chemotherapy with cranial irradiation for prevention of CNS relapse.*

Methods: *From 1998 to 2008 ninety eight cases of acute lymphoblastic leukemia (ALL) admitted in Amirkola Children Hospital were enrolled in this study. The chemotherapy regimen was on the basis of protocol of BFM-79. CNS prophylaxis consisted of intrathecal Cytarabin or Methotrexate, in addition to cranial irradiation for patients more than 3 years old. We assessed the incidence of CNC relapses over 10 years of CNS prophylaxis regimen.*

Results: *From ninety eight cases, 53 were females and 45 were males. Twenty six were below 3 years old and seventy two were above 3 years old ($p<0.05$). For 10 years of study for the 72 cases who were more than 3 years old and had received prophylactic cranial irradiation CNS relapse did not happen. Among the 26 cases below 3 years old who didnot receive prophylactic cranial irradiation CNS relapse for one case happened (3.8%) ($p<0.05$).*

Conclusion: *The results show that the combination of prophylactic CNS irradiation and intrathecal chemotherapy is effective in prophylaxis of CNS relapse in ALL.*

Key words: *Acute Lymphoblastic Leukemia (ALL), CNS relapse, CNS relapse Prophylaxis, Cranial irradiation, Iintrathecal chemotherapy.*

Casp J Intern Med 2010; 1(1): 27- 30

1- Department of oncology & hematology, Babol university of medical sciences, Babol, Iran.
2. pediatric resident, Amirkola hospital, Babol university of medical sciences, Babol, Iran.

*** Correspondence:**
Mohammad Kazem Bakhshandeh Bali (MD), pediatric resident, None – communicable pediatric Diseases Research Center, Amirkola hospital, Babol university of medical sciences, Babol, Iran.
Post Code: 47341-34197
Tel: 0111- 3242151-5
Fax: 0111-2268180
E-mail: mkbakhshandeh@yahoo.com

Received: Jun 20 2009
Revised: Jan 2 2010
Accepted: Jan 30 2010

Although central nervous system (CNS) prophylaxis in patients with ALL has reduced the incidence of CNS recurrence, it still is reported to occur in approximately 5-10% of cases (1). CNS relapse may occur as an isolated event, or in combination with a bone marrow relapse, or with recurrence in another extramedullary site (2). More commonly, the diagnosis of meningeal recurrence is based on a routine examination of CSF. Relapse has been modified over the years, generally accepted criteria has included more than 5 leukocytes per μL, with unequivocal blasts demonstrable in a cytocentrifuge preparation. Although this has been a useful working definition, the significance of blast cells in a cytocentrifuge sample when the CSF leukocyte count is less than or equal to 5 leukocytes per μL is unclear (3). Intensive treatment has recently improved the results for patients with an isolated CNS relapse as high as 70% (4). Although, a decreased incidence of CNS relapse has been observed with prophylaxis, this has not been translated to an improved survival (5,6,7). However, the morbidity associated with CNS disease mandates prophylactic therapy, which is now an integral part of the standard therapy in ALL (8). Several modalities for CNS prophylaxis have been employed including cranial irradiation, intrathecal or intraventricular administration of Methotrexate, Cytarabin and steroids, and high doses of systemic chemotherapy with Dexamethasone, Methotrexate and/or Cytarabin whereby adequate cerebrospinal fluid (CSF) drug levels can be achieved (9-13).

In this study we use Intrathecal chemotherapy and cranial irradiation for ALL cases more than 3 years old and estimate the effect of this prophylactic regimen in prevention of CNS relapse.

Methods

From 1998 to 2008, ninety eight patients admitted in Amirkola Children Hospital (Babol) with Acute Lymphocytic Leukemia (ALL) were enrolled in this study. The morphologic diagnosis was established by microscopic examination on May–Grünwald–Giemsa and cytochemical staining of bone marrow smears, and classified according to the French–American–British (FAB) classification. Immunophenotyping was performed, by indirect immunofluorescence using flow cytometry, focusing on the blast cell population, and employed a panel of monoclonal antibodies to B-cell, T-cell, myeloid, and precursor cell associated antigens (table 1 and table 2). Leukemic cells that expressed none of these markers were considered as undifferentiated. Cytogenetic and eventually molecular analyses were carried out on blood or marrow samples.

The chemotherapy regimens used for two groups consisted of Vincristine, Daunomycin, L-Asparaginase Adriamycin, Cyclophosphamide, 6- Mercaptopurine, Ara.C and Methotrexate was chosen on the basis of BFM-79 protocol. (table.3) In patients with age below 3 years old, CNS prophylaxis consisted of 20-22 times intrathecal chemotherapy with Cytarabin or Methotrexate. Patients with age more than 3 years old received fractionated cranial irradiation prophylaxis by 1800 CGY dosage in addition to intrathecal chemotherapy with Cytarabin or Methotrexate.

Relapse was defined as the reappearance of leukemic cells in the bone marrow with or without clinical evidence of disease. An isolated bone marrow relapse was diagnosed with ≥20% lymphoblasts among nucleated cells in the bone marrow and without evidence of leukemia at extramedullary sites. Accordingly, the isolated extramedullary relapses were those with clinically overt extramedullary manifestation of leukemia especially in the testis and no evidence of bone marrow relapse. CNS relapse was defined as unequivocal morphologic evidence of leukemic blasts in the cerebrospinal fluid (CSF) (14).The follow up of these two groups of patients was history taking and physical examination of radiation adverse effects, and whole blood count (CBC and peripheral blood smear) monthly. We evaluated all cases of ALL who were treated during the year 1998-2008. Categorical variables were compared using t-test and continues variable usere compared by X^2 test.

Results

Fifty three out of 98 cases were female (54%) and 45 were male (46%).Their age range was 10 months old to 13 years. 26 cases were below 3 years (mean age=6 year) and 72 were over this age (mean age= 1.5 year) with mean age of 5 years. 10 patients had leukocyte count more than 50000, 12 cases were above 10 years old, 6 cases were less than one year and 7 (6.1%) patients were diagnosed as T-cell ALL. 69 patients (70.4%) were Early pre B-cell (common ALL), 18 (18.3%) were pre B-cell ALL, 7 (6.1%) were T-cell ALL and 5.2% with other rare immunotypes. 72 patients who were above 3 years and received CNS prophylaxis of intrathecal chemotherapy (Methotrexate or Cytarabin) with prophylactic cranial irradiation, no incidence of CNS relapse was seen. CNS Relapse occurred only in one case (3.8%) ($p<0.05$). 26 patients who were less than 3 years who received CNS prophylaxis of Intrathecal chemotherapy (Methotrexate or Cytarabin) without prophylactic cranial irradiation, CNS relapse occurred only in one case (3.8%).Thus after 10 years diagnosis and treatment of acute Lymphocytic Leukemia patients in this center, the incidence of CNS relapse is about 1%.

Although CNS radiation has worse intellectual, growth and developmental effects, these adverse effects were not seen in any patient after10 years follow up after cranial irradiation. The case of CNS relapse was seen on a 26 months - old boy who was admitted with fever, bone pain, vomiting and headache.CBC at presentation indicated 14500 leukocytes (PMN=30%, lymphocytes=60% and atypical lymphocytes=10%), hemoglobin level of 9.8g/dl and platelet count of 108000. Lymphoblasts were detected in the peripheral blood smear and in bone marrow aspiration which was more than 25% of nucleated cells were Lymphoblasts with L_2 morphology. Immunophenotyping was reported as high population of CD19 (+), Tdt (+) and CD10(+). As mentioned before, this patient did not receive prophylactic cranial irradiation.

Two years after the beginning of chemotherapy and before the termination of protocol therapy (in phase v), he relapsed with presentation of seizure, headache and vomiting. After the diagnosis of CNS relapse, intensive treatment was done with craniospinal radiation and triple Intrathecal chemotherapy (Methotrexate, Cytarabin and hydrocortisone). This patient is alive and under the protocol of CNS relapse chemotherapy.

Discussion

The finding of this study revealed that CNS prophylaxis is very effective to reduce CNS involvement in patient with acute lymphoblastic leukemia. Prophylactic treatment that was used in this study reduced the incidence of CNS relapse in patients with ALL. In the other studies depending on the efficacy of systemic chemotherapy and in the proportion of patients treated initially with cranial irradiation , approximately 5 to 10% of patients with ALL developed isolated CNS relapse (15-17) .There is evidence that if both cranial irradiation and intrathecal chemotherapy are used as CNS prophylaxis in the context of moderately intensive systemic therapy during the initial treatment regimen, the rate of CNS relapse can be reduced to as low as 1 to 2% (18).

In our study the subjects more than 3 years old who received Intrathecal chemotherapy and cranial irradiation had no evidence of CNS relapse and only 3.8% with age below 3 years that received intratecal chemotherapy without cranial irradiation had CNS relapse. Thus with combination of cranial irradiation in our patients, CNS relapse was prevented. Cranial irradiation is an effective CNS-directed therapy. Investigators of the Berlin-Frankfurt-M FC nster group showed that among high-risk patients without a CNS3 status (a nontraumatic cerebrospinal fluid sample that contains 5 WBC/ B5L with identifiable blasts, or the presence of a cerebral mass or cranial palsy), the radiation decreased the incidence of CNS relapse (19).

This study indicate benefits of cranial irradiation and intrathecal chemotherapy for CNS prophylaxis in acute lymphoblastic leukemia that in some studies, cranial irradiation gave better results than intermediate dose of methotrexate (20,21).In an early study, investigators of the Pediatric Oncology Group showed that cranial irradiation could yield results comparable to those achieved with triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabin, and the cranial irradiation could be reduced from 3 years to 1 year in patients with low- risk leukemia (22). Despite the improved treatment for acute lymphoblastic leukemia, CNS prophylaxis remains a therapeutic challenge in childhood ALL, partly because of the late complications arising from cranial irradiation (1, 2).

Combination of CNS radiation prophylaxis has worse intellectual, growth long-term effects, secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity (23-25). Among our patients that received CNS prophylaxis of cranial irradiation, there were no findings of these side effects, because we do not have any significant complain related to conception and education. To avoid irradiation toxicity in the children younger than 3 years, a treatment without radiation should have to be considered.

Conclusion

This study shows that the combination of prophylactic CNS irradiation and Intrathecal chemotherapy is effective in prophylaxis of CNS relapse in acute lymphoblastic leukemia.

References

1. Bleyer WA, poplack DG. Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin oncol 1985; 12: 131- 48.
2. George SL, Ochs JJ, Mauer AM, Simone JV. The importance of an isolated central nervous system relapses in children with acute lymphoblastic leukemia. J Clin oncol 1985; 3: 776- 781.
3. Lauer SJ, Kirchener PA, Camitta BM. Identification of leukemic cells in the cerebrospinal fluide from children with acute lymphoblastic leukemia: advances and dilemmas. Am J Pediatr Hemato oncol 1989; 11: 64-73.
4. Ribeiro RC, Rivera GK, Hudson M, et al. An intensive re-treatment protocol for children with an isolated CNS relapse of acute lymphoblastic leukemia. J Clin oncol 1995; 13: 333- 8.
5. Lauer S, Shuster J, Kirchener PA, et al. Prognostic significance of cerebrospinal fluid (CSF) lymphoblasts (LB) at diagnosis (dx) in children with acute lymphoblastic leukemia (ALL). Proc Am Soc Clin Oncol 1994; 13: 317.
6. Berger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid (CSF) examination in children with acute lymphoblastic leukemia (ALL) significance of low leukocyte

counts with blasts or traumatic lumbar puncture. J Clin Oncol. 2003; 21: 184-8.

7. Nachman J, Cherlow J, Sather HN, et al. Effect of initial central nervous system (CNS) status on the event-free survival (EFS) in children and adolescents with acute lymphoblastic leukemia (ALL). Med Pediatr Oncol 2002; 39: 277.
8. Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: a CLCG-EORTC report. Leukemia 2000; 14: 2257-66.
9. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not predict for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: a Childres Cancer Group report. J Clin Oncol 1994; 12: 2594-600.
10. te Loo DM, Kamps WA, Does-van den Berg AV, van Wering ER, de Graaf SS. Prognostic significance of blasts in the cerebrospinal fluid without pleiocytosis or a traumatic lumbar puncture in children with acute lymphoblastic leukemia: the experience of the Dutch Childhood Oncology Group. J Clin Oncol 2006; 24: 2332-6.
11. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children Research Hospital. Blood 2004; 104: 2690-6.
12. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared to intrathecal 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: 1165-73.
13. Gajjar A, Harrison PL, Sandlund JT, et al. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. Blood 2000; 96:3381-4.
14. Silverman LB, Declerck L, Gelber RD, et al. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981-1995). Leukemia 2000; 14: 2247-56.
15. Mahmoud HH, Rivera GK, Hancock ML, et al. Low leukocyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. N Engl J Med 1993; 329: 314-9.
16. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 2002; 99: 863-71.
17. Kantarjian HM, O 92Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000; 18: 547-61.
18. Raje Ns,Vaidya SJ, Kapoor G, et al. Lowincidence of CNS relapse with cranial radiotherapy and intratechal methotrexate in acute lymphoblasticc leukemia. Indian Pediatr 1996; 33: 556-60.
19. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. Blood 2000; 95: 3310-22.
20. Freeman AI, Weinberg V, Brecher ML, et al. Comparison of intermediate-dose methotrexate with cranial irradiation for the post-induction treatment of acute lymphocytic leukemia in children. N Engl J Med 1983; 308: 477–84.
21. Riehm H, Gadner H, Henze G, et al. Results and significance of six randomized trials in four consecutive ALL - BFM studies. Haematol Blood transfus 1990; 33: 439–50.
22. Sullivan MP, Chen T, Dyment PG, Hvizdala E, Steuber CP. Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a Pediatric Oncology Group Study. Blood 1982; 60: 948-58.
23. Pui CH, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med 2003; 349: 640-9.
24. Ochs JJ. Neurotoxicity due to central nervous system therapy for childhood leukemia .Am J Pediatr Hematol Oncol 1989; 11: 93-105.
25. Waber Dp, Urion DK, Tarbell NJ, et al. Late effects of central nervous system treatment of acute lymphocytic leukemia in childhood are sex-dependent. Dev Med Child Neurol 1990; 32: 23