Central Nervous System Relapse in Acute Lymphoblastic Leukemia (Study on 160 cases)

Azarm T.[1,*], Jahani M.[2], Amini A.Gh.[1], Saghfi M.R.[1]
[1]Saied-alshohada Medical Center; Isfahan University of Medical Siences; Islamic Republic of Iran.
[2]Hematology- Oncology and Bone Marrow Transplantation Research Center, Tehran University of Medical Sciences
[*]Corresponding author

Abstract

From 1365 to 1382, 205 cases of Acute lymphoblastic leukemia (ALL) were refered to our Center. 160 cases achived complete remission and entered our clinical trial of CNS relapse which were under consideration. The patients included 98 men and 62 women with an average age of 32 years (range 4-61 years). 160 of 205 cases had complete remission with a rate about 78%.The latter group was entered into our clinical trial. The patients were followed for 30 months after starting maintenance therapy. All patients underwent CNS prophelaxy by CNS Irradiation with 14 GY and Intratechal Methotrexate injection for 6 weeks. 24 cases had relapsed. The age of CNS relapsed patients were between 9 to 58 years (Mean 31y). Patient Sex: 11 male of 91, 13 female of 69.

Results: 1 case showed CNS relapse after 4 months of starting maitenance therapy. 19 cases relapsed in the duration of 6-18 months after starting maintenance therapy. 2 cases relapsed within 24 & 28 months after starting maintenance therapy. The Statistic analysis are summarized as follows:

1-CNS relapse of ALLin the Females are more than Males (p=0.001).
2-CNS relapse of ALL in the age groupe older than 12 years were higher.
3-CNS relapse of ALL in those patients with bone marrow failure in responding to first period of treatment were higher (p=0.002).
4-CNS relapse of ALL in those patients with Leukocytosis more than 40.000/ul were higher (p=0.003).
5-The first Symptom of CNS relapse was severe headache (100%).
6-CNS relapse of ALL were in 18 months period of strating maintenance therapy.
7-CNS relapse of ALL in those patients with Type II ALL were more than Type I, with a rate of 18.7 % and 4.7% respectively.

Key Words: Acute Lymphoblastic Leukemia, CNS– relapse

Received: 10, Nov., 2004
Accepted: 22, Jan., 2005

Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent neoplastic disease in childhood and accounts for about 20 percent of acute leukemias in adults[(1)].An early peak of ALL incidence occurs at the age of 3 to 4 years and about one-fourth of patients are aged 15 years or more. ALL is relatively infrequent in younger adults, but the incidence seems to increase in adults aged over 40 to 50 [(1,2)].The median age of patients in most reports of therapy of adults ALL ranges from 25 to 37 years. Although a small percentage of cases are associated with inherited genetic syndromes, the cause of ALL remains largely unknown.[(3)] Seventy-five to 80% of patients with ALL attain remission and survive free of leukemia recurrence at least 5 years from diagnosis with current treatments that incorporate systemic therapy (e.g., combination chemotherapy) and specific central nervous system (CNS) preventive therapy (i.e., intrathecal chemotherapy with or without cranial irradiation).[(4,5)]

Morphology

Morphologic classification of ALL is ofen based upon the French-American-British (FAB) system. According to this system[(6,7)].

▪ L1 lymphoblasts are small cells with scant cytoplasm, condensed nuclear chromatin, and indistinct nucleoli. Most cases (85 to 89 percent) of ALL in children are classified as FAB L1.[(7)]

▪ L2 lymphoblasts are larger cells with a moderate amount of cytoplasm, dispersed chromatin, and multiple nucleoli. In some studies, L2 has been associated with worse prognosis than has L1. Most patients are adult and 11 to 14 percent of cases of ALL in children are classified as FAB L2.(7)

▪ L3 lymphoblasts have deep cytoplasmic basophilia with prominent cytoplasmic vacuolation. L3 morphology correlates with a more guarded prognosis. The L3 cell usually has mature B-cell characteristics and is ofen treated using drugs effective for highly aggressive B-cell lymphoma variants. Most patients are adult and less than one percent of cases of ALL in children are classified as FAB L3.(7,8)

The aims of modern ALL treatment regimens are:

Rapid restoration of bone marrow function, using multiple chemotherapy drugs at acceptable toxicities, in order to prevent the emergence of resistant subclones.

▪ Use of adequate prophylactic treatment of sanctuary sites such as the central nervous system (CNS), since CNS relapse is associated with a poor prognosis.(4,9)

▪ Postremission consolidation therapies to eliminate minimal (undetectable) residual disease. Postremission therapy has traditionally been categorized as intensification or consolidation treatment, and prolonged maintenance.(8,9)

CNS Status at Diagnosis

CNS status at diagnosis has prognostic significance.[7] Patients who have a nontraumatic diagnostic lumbar puncture may be placed into 3 categories according to their CNS status: (10,11)

- **CNS1:** CSF<5 WBC/μL with cytospin negative for blasts.
- **CNS2:** CSF<5 WBC/μL with cytospin positive for blasts.
- **CNS3:** CSF≥5 WBC/μL with cytospin positive for blasts.

Patients with ALL who present CNS disease at diagnosis (i.e., CNS3) are at higher risk for treatment failure (both within the CNS and systemically) compared to patients not meeting the criteria for CNS disease at diagnosis. Patients with small numbers of leukemic cells in the cerebrospinal fluid below those required for a diagnosis of CNS disease (i.e., CNS2) may be at increased risk of CNS relapse.(12,13) In patients with neurologic infiltration with ALL, an important benefit of aggressive treatment is the potential for long-term survival. In these patients, however, the late complications of radiation treatment can be profound and debilitating.(14,15)

Patients and method

205 patients with acute lymphoblastic leukemia (ALL) who attended the Saied-al Shohada medical center (Esfahan University of Medical Sienses) between Septamber1986 and March, 2003 were treated for induction therapy. 160 cases responsed and achieved complete remission and entered to our study which evaluated for CNS relapse of ALL.

ALL was diagnosed with peripheral blood smear (PBS) and bone marrow smear (BM) histologic examination.In 87 cases the diagnosis was confirmed by Flowcytometry and in 38 cases by cytochemical staining. The patients included 98 men and 62 women with a mean age of 31 years (range 5-61 years). The type of ALL included 31 type I, 107 type II, and 32 type III (FAB classification). After starting two or three courses induction therapy all patients (after achieved remission) underwent lumbar puncture (LP) and cerebrospinal fluid cytologic examination with gemsa staining. There are different opinions as to when the first lumbar puncture should be done. One procedure is to delay the examination until remission is achieved, in order to avoid seeding of the CNS by circulating leukemia blast cells from the peripheral blood.(11) After the final consolidation therapy,all patients underwent another lumbar Puncture and cytologic examination on cerebrospinal fluid to exclude CNS involvement. CNS prophelaxia with 6 courses of intrathecal injection of Methotrexate (10 mg/m) with CNS radiotherapy were performed. LP was repeated every three month, and when the patients had headache or any symptom or sign of CNS. We investigated the associations between CNS relapse in ALL in complete remission and the types of ALL within significant reductions in risk of CNS relapse were observed for patients.

Results

205 patients with acute lymphoblastic leukemia (ALL) were treated with chemotherapy.45

of them did not respond to treatment and no achieved complete remission and the rest patients (160 of 205) cases had complete remission with percentage of about 78%. The latter group (160 patients) were entered into our clinical trial and followed for exclution or confirmation of initial CNS relapse. Among 160 consecutive patients monitored during first complete remission, central nervous system leukemia developed in 24 cases (15%). In One patient CNS involvement was detected after four months of starting maintenance therapy. 19 cases were detected to have CNS relapse in the duration of 6-18 months after starting maintenance therapy. 4 cases relapsed in the duration of 24–28 months after maintenance therapy. The patients were followed for 30 months after starting maintenance therapy.

18 of 24 CNS relapsed patients showed bone marrow relapse following detection of CNS relapse.

CNS relapse acording to type of ALL: In Type II ALL 20 0f 107 (18, 7%), in type I ALL one of 21 (4.7 %), and in type III 3 of 32 (9.4 %) relapsed.

The Statistical analysis are summarized as follows:

1-CNS relapse of ALL in Females was 13 cases of 6 cases (18 %) and in Males 11 cases of 91 (12%). (p=0.003)

2-CNS relapse of ALL in older than 18 year group was higher (p=0.001).

3-CNS relapse of ALL in patients with bone marrow failure in response to first period of treatment was higher. (p=0.001)

4-CNS relapse of ALL in those patients with Leukocytosis more than 40.000 /ul was higher. (p=0.001)

5-The first Symptom of CNS relapse was severe refractory headache with the rate of 100%.

6-CNS relapse of ALL in the 18 month period of strarting maintenance therapy was higher with a rate of 19 of 24 (79%).

Discussion

To identify patients with acute lymphoblastic leukemia at risk for the development of central nervous system involvement, we performed periodic cerebrospinal fluid examination of patients in remission. Among 160 consecutive patients monitored during first complete remission, central nervous system leukemia developed in 24 cases (15%). CNS relapse of ALL in the females was more than Males (p=0.003). Acording to Ching-Hon Pui's study (17) there were no significant differences in CNS relapse rate between the two sexes. In other studies, girls clearly faired better than boys on treatment and achieved remission[18,19], but nothing was mantioned about the rate of CNS relapse in both sexes.

CNS relapse of ALL in patients with bone marrow failure in response to first period of induction treatment, and in those patients with Leukocytosis more than 40.000 /ul, was higher. Factors at diagnosis associated with the subsequent development of central nervous system leukemia were elevated leukocyte count, elevated serum lactate dehydrogenase, extramedullary infiltration including splenomegaly and hepatomegaly.[10,18] The most important risk factors for CNS relapse were ALL; type II ALL more than type I ALL (18.7 %. 4.7%) respectively.

The effect and different treatment as a CNS prophelaxy with injection of intrathecal Methotrexate and Methotrexate plus cranial radiotherapy still require further evaluation to determine which treatments are damaging, how severe the long-term effects are, and which subgroups of children and adolescent patients are most affected. Recent nonrandomized comparisons of patients receiving chemotherapy regimens plus X- ray therapy with patients receiving chemotherapy alone, and with healthy controls. indicate that X- ray therapy causes learning problems[15,17,18,19] .One retrospective comparison of children from a randomized trial of X ray therapy versus intermediate-dose IV Methotrexate showed poorer long- term psychosocial functioning with X- ray therapy.[14,15]

We find that male patients continue to be at higher risk for hematologic, but not extramedullary. Relapse compared to the probablitity of these events in female patients. The CNS relapse rate in female and male patients was 17.7%, 13.2% respectively. Although in male ALL patients testicular relapse was high in the early treatment and is not negible in such patients.

In conclusion, central nervous system leukemia developed in 15% of cases. Use of adequate prophylactic treatment of sanctuary sites such as the central nervous system (CNS), since

CNS relapse is associated with a poor prognosis. The Periodic LP examination of the cerebrospinal fluid (CSF) and cytologic examination on cerebrospinal fluid is an essential diagnotic procedure in ALL to exclude or confirm CNS relapse. X ray therapy (for CNS prophelaxy) can be replaced by long–term intrathecal therapy without detriment to event-free survival (EFS) or overall survival for CNS prophelaxy for children and adolescent patients with ALL.

References:

1. Pui C-H, Evans WE: Acute lymphoblastic leukemia. N Engl J Med 339:605-615.1998.
2. Terzah M Horton, MD, PhD. C Philip Steuber, MD.: Overview of the presentation and classification of acute lymphoblastic leukemia in children. Up To Date. 0nline 13.1 .2005
3. McNeil, DE, Cote, TR, Clegg, L, Mauer, A. SEER update of incidence and trends in pediatric malignancies: acute lymphoblastic leukemia. Med Pediatr Oncol 2002; 39:554.
4. Richard A Larson.MD: Treatment of acute lymphoblastic leukemia in adults. UpToDate. 0nline 13.1 .2005.
5. Hjalgrim, LL, Rostgaard, K, Schmiegelow, K, et al. Age- and sex- specific incidence of childhood leukemia by immunophenotype in the Nordic countries. J Natl Cancer Inst 2003; 95:1539.
6. C.H.Pui, M.Schrappe, R.C. Ribeiro, and C.M.Niemeyer: Childhood and Adolescent Lymphoid and Myeloid Leukemia. Hematology, January 1,2004; 2004(1): 118-145.
7. Miller, DR, Leikin, S, Albo, V, et al. Prognostic importance of morphology (FAB classification) in childhood acute lymphoblastic leukaemia (ALL). Br J Haematol 1981; 48:199.
8. Fenaux P.Bourthis JH, Ribrag V.: Burkitt's acute lymphocytic leukemia (L3 ALL) in adults. Hematol Oncol Clin North Am.2001 Feb; (1):37-50.
9. D.P.Waber,L.B. Silverman, L.Catania, W. Mautz, M. Rue, R.D.Gelberet al.: Outcomes of a Randomized Trial of Hyperfractionated Cranial radiation Therapy for Treatment of High-Risk Acute Lymphoblastic Leukemia: Therapeutic Efficacy and Neurotoxicity.J.Clin.Oncol., July 1,2004; 22(13): 2701-2707.
10. Jaing TH, Yang CP, Hung IJ, Tasy PK, Tseng CK, Chen SH.: Clinical significance of central nervous system involvement at diagnosis of cell acute lymphoblastic leukemia.pediatr Blood Cancer.2005 Feb 9.
11. Britta Burger, Martin Zimmermann, Georg Mann, Joachim Kuhl, Lutz Loning, Hansjorg Riehm, Alfred Reiter, Martin Schrappe: Diagnostic Cerebrospinal Fluid Examination in children with Acute Lymphoblastic Leukemia: Significance of Low Blasts or Traumatic Lumbar Puncture. Journal of Clinical Oncology,Vol 21, Issue 2 (January), 2003:184-188.
12. Brunning, RD, Flandrin, G, Borowitz, M, et al. Precursor B lymphoblastic leukaemia/lymphoblastic lymphoma (Precursor B-cell acute lymphoblastic leukaemia). In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Jaffe, ES, Harris, NL, Stein, H, Vardiman, JW (Eds), IARC Press, Lyon, 2001. p.111.
13. Surapaneni UR, Cortes JE, Thomas D, O'Brien S, Giles FJ, Koller C, Faderl S, Kantarjian H.: Central nervous system relapse in adults with acute lymphoblastic leukemia. Cancer.2002 Feb 1; 94(3):773-9.
14. Christine Sharis MD. Complication of cranial irradiation. UpToDate. 0nline 13.1 .2005.
15. Spiegler, BJ, Bouffet, E, Greenberg, ML, et al. Change in neurocognitive functioning after treatment with cranial radiation in childhood. J Clin Oncol 2004; 22:706.
16. M.Clarke,P. Gaynon,I.Hann,G.Harrison,G. Masera,R.Peto,and S.Richared.:CNS-Directed Therapy for Childhood Acute Lymphoblastic Leukemia: Childhood ALL Collaborative Group Overview of 43 Randomized Trials.Journal of Clinical Oncology,Vol 21, No 9 (may 1),2003: pp 1798-1809.
17. C.-H.Pui. Toward Optimal Central Nervous System-Directed Treatment in Childhood Acute Lymphoblastic Leukemia. J.Clin.Oncol., January 15, 2003; 21(2): 179-181.
18. Oeffinger KC, Mertens AC, Sklar CA, et al.: Obesity in adult survivors of childhood acute lymphoblastic leukemia: A report from the childhood cancer survivors study.J Clin Oncol 21: 1359-1365, 2003.
19. Virginia Kimball Dalton, Montse rue, Lewis B.Silverman, Richard D et al.: Height and Weight children Treated for Acute Lymphoblastic Leukemia: Relationship to CNS Treatment. Journal of Clinical Oncology,Vol 21, issue 15 (August), 2003 :2953-2960.