Central nervous system relapse prophylaxis in acute lymphocytic leukemia: intrathecal chemotherapy with and without cranial irradiation

Abstract

**Background:** Central nervous system (CNS) relapse in acute lymphocytic leukemia was significantly decreased due to the use of new chemotherapeutic 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, 98 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 cytarabine 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 three years old (p<0.05). For the 10 years of study in 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 did not 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 Lymphocytic Leukemia (ALL), CNS relapse, CNS relapse Prophylaxis, Cranial irradiation, Intrathecal chemotherapy.

Although the 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% 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 cerebrospinal fluid (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 ≤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 (5-7). 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, cytarabine and steroids, and high doses of systemic chemotherapy with dexamethasone, methotrexate and/or cytarabine whereby adequate cerebrospinal fluid 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 the 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 flowcytometry, 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 CSF. 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. Categorical variables were computed using t-test and continues variable user compared by X² 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. Twenty-six cases were below 3 years (mean age of 1.5 years) and 72 were over this age (mean age of 6 years). Ten 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.

Sixty nine 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. Seventy two 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). Twenty six patients less than 3 years who received CNS prophylaxis of intrathecal chemotherapy without prophylactic cranial irradiation, CNS relapse occurred only in one case (3.8%). Thus, after 10 years of diagnosis and treatment of acute lymphocytic leukemia patients in this center, the incidence of CNS relapse was about 1%.

Although CNS radiation has worse intellectual, growth and developmental effects, these adverse effects were not seen in any patient after 10 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 9.8 g/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 was lymphoblasts with L₂ 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
arising from cranial irradiation in childhood ALL, partly because of the late complications of leukemia, CNS prophylaxis remains a therapeutic challenge.

Despite years to 3 cytarabine, and could yield results comparable to those achieved with triple therapy. Investigators of the Pediatric Oncology Group showed that 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 cytarabine, 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).

**Discussion**

The finding of this study revealed that CNS prophylaxis is very effective to reduce CNS involvement in patient with acute lymphocytic 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, those subjects more than 3 years old who received intrathecal chemotherapy and cranial irradiation had no evidence of CNS relapse and only 3.8% with the age below 3 years that received intrathecal 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 n ster group showed that among high-risk patients without a CNS status (a nontraumatic cerebrospinal fluid sample that contains 5 WBC/BSL with identifiable blasts, or the presence of a cerebral mass or cranial palsy), the radiation decreased the incidence of CNS relapse (19).

This study indicates 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 cytarabine, 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 may worsen 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 the 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. In conclusion, our results show that the combination of prophylactic CNS irradiation and Intrathecal chemotherapy is effective in prophylaxis of CNS relapse in acute lymphoblastic leukemia.

**References**


