Central Nervous System Relapse in acute Lymphoblastic Leukemia: Prognostic Factors and the Outcome

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ABSTRACT:

BACKGROUND:

Despite the advances in treatment of acute lymphoblastic leukemia(ALL), CNS relapse remains an obstacle to successful treatment. This study was performed to determine the frequency of CNS relapse in ALL patients and to study risk factors and outcome after CNS relapse.

PATIENTS AND METHODS:

A retrospective study done on 364 patients diagnosed as ALL in Central Teaching Hospital for Children-Baghdad for the period from 1st Jan 2000 to 31st Mar 2005. ALL patients whom diagnosed after 1st Jan 2004 received CTHC 2004 protocol .The following parameters were studied: gender, age, hepatomegaly, splenomegaly, LAP, mediastinal mass, initial WBC count, platelets count, FAB morphology, initial CNS involvement and if the patient received radiotherapy.

RESULTS:

35 patients were excluded from the study. Out of 329 eligible patients, 76 patients (23.1%) had CNS relapse(isolated or combined), with mean duration before CNS relapse 12.30±8.28 months and median of 11 months. The following factors were significantly associated with development of CNS relapse: male gender, age <2 years, massive hepatomegaly, massive splenomegaly, lymphadenopathy, mediastinal mass, initial WBC count≥50000/mm, initial CNS involvement, and patients who did not receive prophylactic CNS radiation. The study shows that frequency of CNS relapse decreased significantly after addition of three intrathecal doses during induction). Shorter duration between diagnosis of ALL and CNS relapse was associated with higher mortality.

CONCLUSION:

Frequency of CNS relapse and mortality rate still higher than globally-accepted figures. Intensification of systemic and CNS-directed therapy, significantly decreased these figures in our patients.

KEY WORDS : CNS relapse, leukemia, children, prognosis.

INTRODUCTION:

Despite the advances in treatment of childhood ALL, overt meningeal leukemia remains a dire condition. [1] Some of blast cells, which reside in CNS, hide from chemotherapy (except steroids) by the effect of Blood brain barier[2])

By the early 1970s, the frequency of CNS leukemia in some studies ranged as high as 80% to 85%,[3] but the administration of 2400 cGy cranial irradiation plus five concurrent doses of intrathecal methotrexate or 2400 cGy of craniospinal irradiation alone reduced the incidence of CNS relapse to approximately 10%.[4] However, with long-term follow-up of large numbers of children, it became apparent that there were late adverse effects, including growth and endocrine problems [5] an increased risk of developing secondary tumors[6,7] and possible neuropsychological sequelae.[8] Many pediatric protocols in this era restrict the use of cranial radiation to patients with a higher risk of meningeal relapse, especially those with T-cell disease, high presenting WBC count, or overt CNS leukemia at diagnosis.[9,10] With current approaches, approximately 2% to 10% of patients can be expected to develop CNS relapse.[11,12]

PATIENTS AND METHODS:

A retrospective study was done on 364 patients who were admitted to the Central Teaching Hospital for Children (CTHC) / Baghdad-Hematology and Oncology Unit and was diagnosed as acute lymphoblastic leukemia (ALL) in the period from 1st Jan, 2000 to 31st Mar, 2005 depending on their medical records. The minimal period for follow-up was 12 months.

Diagnosis of ALL was established according to clinical manifestations, results of CBC and BM aspirate examination using light microscopy and applying FAB morphologic classification.[13] Unfortunately, histochemical stains, immunophenotyping, chromosomal studies and

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molecular biology studies were not available during the period of study.

Patients who were diagnosed as ALL from 1st Jan, 2000 to 31st Dec, 2003 were treated as following:

A-Induction phase: VCR, prednisolone and L-asparginase.

B-Induction of remission was followed by CNS prophylaxis with four intrathecal weekly doses of MTX. Cranial radiation was given later on for most of the patients.

C- Consolidation cycles (4 cycles every other week):

Ara-C and 6-TG

D- Maintenance of remission: 6-MP and oral MTX

Total duration for treatment was 3 years

From 1st Jan, 2004 to 31st Mar, 2005, ALL patients were treated according to CTHC 2004 ALL protocol which includes the following for standard-risk patients:

A-Induction :- VCR, Prednisolone, L-asparaginase and triple intrathecal therapy

B-Consolidation (4 cycles given every other week): Ara-C, 6-MP, IV MTX

C-CNS prophylaxis (4 intrathecal doses given weekly): Triple intrathecal therapy and prophylactic radiotherapy for patients > 2 years of age

D-Maintenance: 6-MP and MTX and three-monthly doses of VCR, prednisolone, and triple intrathecal therapy

Total duration of therapy was 3 years

High-risk patients were categorized when have one or both of the following criteria:

1. Age<2 year or >10 years

2. WBC count >50000/mm[(13)]

The high-risk protocol included:

A-Induction: same as in standard-risk in addition to Adriamycin

B-Intensification cycles (2 cycles, 2 weeks apart): Ara-C, Etoposide, L-asparaginase, VCR and Prednisolone

C-Consolidation cycles: same as in standard-risk

D-CNS prophylaxis: same as in standard risk

E-Maintenance: same as in standard risk

Total duration of therapy is 3 years.

CNS relapse was diagnosed when patients in 1st complete remission (CR1) had blasts in CSF or abnormally high WBC count and high protein and low glucose in CSF[(13)] with clinical evidence of CNS involvement (e.g., headache and vomiting, meningeal irritation signs, cranial nerves palsies, seizures, or hypothalamic syndrome) or a cerebral mass detected by CT scan. Initial CNS involvement was diagnosed when the first CSF examination included blast cells or had abnormally high WBC count with clinical signs mentioned above.

The following parameters of each ALL patient were studied: gender, age at diagnosis, massive hepatomegaly (>4 cm below costal margin), massive splenomegaly (>3cm below costal margin), significant lymphadenopathy (LAP), mediastinal mass (>1/3 of thoracic diameter at T5), [(33)]initial peripheral total WBC count, initial platelets count, morphologic subtype of ALL according to FAB classification and first CSF result.

Associated clinical findings with CNS relapse (e.g., headache, vomiting, meningeal irritation signs, blurred vision, etc.) were studied.

Patients who died or lost follow-up during induction were excluded from the study.

For statistical analysis, we used Chi-square test at 95% confidence interval, Mantel-Haenzel Chi-square test and student's t-test. A P-value of <0.05 was considered indicative of statistically significant difference.

RESULT:

During the period from 1st Jan, 2000 to 31st Apr, 2005, total number of ALL patients was 364 (males=211, females=153). Patients who died or lost follow-up during induction were excluded from this study. They were 35 patients (males=14, females=21). Four of them had initial CNS involvement and they died.

Out of the eligible 329 patients, 76 patients (23.1%) had CNS relapse (isolated CNS relapse=42 patients (55.3%), combined CNS and medullary relapse=34 patients (44.7%)), with mean duration between initial diagnosis of ALL and CNS relapse was 12.30±8.28 months (median=11 months).

Some of the initial clinical and laboratory criteria and their effect on future development of CNS relapse are shown in table 1.

Table 1: Clinical and initial laboratory characteristics as risk factors to develop CNS relapse.

Criteria	Total (n=329)	Number of patients who had CNS relapse (%)	P-value
Gender Male Female	 197 132	 56 (28.5) 20(15.2)	<0.01$
Age <2 2-10 >10	 31 244 54	 13(42) 52 (21.3) 11 (20.3)	<0.05$
Hepatomegaly	184	53 (28.8)	<0.01$
Splenomegaly	140	43 (30.7)	<0.005$
LAP	131	41(31.3)	<0.005$
Mediastinal mass	25	12(48)	<0.005$
Initial WBC ≥50000/mm^3	64	28(43.75)	<0.0005$
Initial platlets <20000/mm^3	158	43(27.2)	>0.05
FAB subtype* L1 L2 L3	 143 161 7	 39(27.3) 36(22.4) 1(14.3)	>0.1
Initial CNS involvement	20	14(70)	<0.0000005$

*18 patients have no report of FAB subtype.
$: statistically significant

Prophylactic cranial irradiation:
It was part of treatment protocol for our patients. For 50 patients, there were no reports whether they received prophylactic radiation or not. Out of them, 11 patients developed CNS relapse. For the remaining patients, some of them did not receive prophylactic cranial irradiation because either the family refused the radiation or the patient was less than 2 years of age. Table 2 shows the results of prophylactic cranial irradiation in preventing CNS relapse.

Table 2: Prophylactic cranial irradiation and CNS relapse.

Status	No CNS relapse (%)	CNS relapse (%)	Total
Not received cranial RT	79 (64.2%)	44 (35.8%)	123
Received cranial RT	135(86.5%)	21 (13.5%)	156
Total	214	65	279

P<0.00005 (significant)

Frequency according to year of diagnosis:
Figure 1 shows the frequency of ALL patients over the years 2000 to 31st Mar, 2005. Also it shows the frequency of CNS relapse in those patients and those relapsed within 12 months of diagnosis.

Table 3 shows the frequencies of CNS relapse in ALL patients diagnosed before and after 2004 in CTHC. Table 4 shows the frequencies of CNS relapse within 12 months for these patients.
* From 1st Jan to 31st Mar 2005

Table (3):Frequency of CNS relapse for patients treated before and after 2004.

Time of diagnosis	No CNS relapse (%)	CNS relapse (%)	Total
Patients diagnosed and treated before 2004	197(74.1%)	69 (25.9%)	266
Patients diagnosed and treated after 2004*	56(88.9%)	7 (11.1%)	63
Total	253	76	329

P<0.01 (significant)
* CTHC 2004 ALL protocol

Table (4): Frequency of CNS relapse within 12 months before and after 2004.

Time of diagnosis	No CNS relapse within 12 months (%)	CNS relapse within 12 months (%)	Total
Patients diagnosed and treated before 2004	223 (83.8%)	43 (16.2%)	266
Patients diagnosed and treated after 2004*	59 (93.7%)	4 (6.3%)	63
Total	282	47	329

Mantel-Haenszel X^2 test=4.00 O.R.=0.35 P<0.05 (significant)

Frequency of clinical features:-
Some clinical features were observed at the time of diagnosis of CNS relapse as shown in table 5. 10 patients (13.1%) of CNS relapse patients were asymptomatic (discovered during routine L.P. for intrathecal prophylaxis).

Table 5: Frequency of clinical features in CNS-relapsed patients.

Clinical Feature	Number	Percenatge (%)
Headache	25	32.8
Facial palsy	21	27.6
Vomiting	15	25
Meningeal irritation signs	13	17.1
Asymptomatic	10	13.1
Squint	10	13.1
Blurred vision or blindness	5	6.5
Hypothalamic syndrome	4	5.2
Seizures	4	5.2
Bulbar palsy	2	2.6
Hemiplagia	1	1.3

Follow-up after CNS relapse:

23 patients with CNS relapse (30.2%) developed BM relapse after a mean duration ± S.D. of 7.86±9.84 months (median=3 months) from CNS relapse. Three of them still alive.

The mean duration between initial diagnosis of ALL and CNS relapse in patients who developed BM relapse after CNS relapse were 11.17±7.61 months while the mean duration for patients who did not develop BM relapse after CNS relapse was 13.26±8.87 months (student's t-test=0.93, P>0.1 , not significant).

Mortality rate after CNS relapse in our study was 72.3% (55 patients). Mean duration±S.D. between CNS relapse and death was 7.72±8.62, median 4 months and range 0-34 months.

Mean duration±S.D. between diagnosis of ALL and CNS relapse in patients who died or still alive was 10.56±7.27 months vs 20.42±8.50 months (student's t-test=19.11, P<0.00005, significant)

Three patients out of 56 males who developed CNS relapse (5.3%) had previous testicular relapse, and 5 patients (7.1%) had testicular relapse after CNS relapse.

Seven patients lost follow up after CNS relapse. Mean duration between diagnosis of ALL and CNS relapse for them was 9.71±5.82, median = 9 months.

DISCUSSION:

Frequency of CNS relapse in ALL patients enrolled in our study was 23.1% (76 out of 329 patients) which is higher than most of other recent studies as they detected less than 10% for all ALL patients[14,15] and less than 5% for standard risk patients.[16,17] This difference might be due to less intensive regimens of CNS-directed therapy adapted in our center (only 4 intrathecal doses of MTX for patients diagnosed before 2004 and 7 intrathecal triple chemotherapy doses for patients diagnosed after 2004 plus cranial irradiation). Extended intrathecal therapy and systemic HD-MTX or Ara-C couldn't be given in our center because of shortage or lack of supportive measures required for such management (e.g., measurement of MTX blood level, etc). Other reasons for this high percentage of CNS relapse cannot be excluded! (e.g., unavailability of further diagnostic procedures like immunophenotyping, poor compliance by the parents, questionable laboratory results, etc.).

Some literatures documented that early intensification of adequate CNS prophylaxis is critical in achieving control of sanctuary disease.[18,19] High-risk groups of ALL can achieve high event-free survival with intensive protocols that omit cranial irradiation.[10,14] .

There was a significant male predominance (28.5% vs 15.2%, P<0.01) in patients who developed CNS relapse. This result is similar to results of other studies.[1,4] Male gender is a known risk factor in ALL due to more T-cell disease and other factors like genetic, metabolic and endocrine factors that contribute to this effect. [13]

Stratification of patients according to age showed that patients who were less than 2 years of age at diagnosis might have more likelihood to develop CNS relapse. For note, these patients didn't receive prophylactic irradiation. Moricke et al[20] proposed that age in pediatric ALL may have an independent prognostic impact. However, their analysis showed that the age-associated different prognosis is at least partly related to the different distribution of relevant prognostic subgroups between the age groups.

Morphologic subtype of ALL according to FAB classification had no influence on frequency of CNS relapse in our study. Hammond et al[21] .concluded that L2 morphology lost its significant impact on outcome of ALL when adjusted for other independent risk factors.

Lymphomatous presentation (massive hepatomegaly, massive splenomegaly, and significant lymphadenopathy) and particularly mediastinal mass were all associated significantly with later development of CNS relapse. Similar results were published in other literatures.[22,23]

Leukemic infiltration of the thymus gland appears as an anterior mediastinal mass on a chest radiograph. It is observed in about 10 percent of patients with newly diagnosed ALL and is nearly always associated with the T-cell immunophenotype.[13] .

Another highly significant risk factor to develop CNS relapse in this study was initial WBC count >50,000/mm^3 (28 patients, 43.75%; vs 48 patients, 18.1%; P<0.0005) . This finding was documented by others.[14,21,24].

Initial platelets count <20,000/$mm^{(3)}$ was reported to be associated with significant incidence of CNS relapse, as this may lead to microhemmorhages.[24,25] We failed to document this association in our study (43 patients, 27.2% vs 33 patients, 19.2%; P>0.05).

Initial CNS involvement in ALL patients was highly associated with later development of CNS relapse after achieving complete remission. This highly significant finding was detected in other studies.[15,26]

Patients who got the opportunity to receive prophylactic cranial irradiation had much lower chance of CNS relapse (13.5% vs 35.8%, P<0.00005). Cranial irradiation was an important part of CNS-preventive therapy in many protocols

since early 1970s.[4] However, a recent collaborative meta-analysis concluded that cranial irradiation can be replaced by long-term intrathecal therapy without detriment to event-free survival.[10].
For patients who were diagnosed during the years 2000 through 2003, when no prophylactic intrathecal therapy during induction phase was given, the frequency of CNS relapse was significantly higher than those patients who were diagnosed and treated according to the newer CTHC protocol (i.e., additional 3 doses of intrathecal triple chemotherapy during induction and intensification of systemic chemotherapy), (25.9% vs 11.1%, P<0.01). Even when we compared the frequency of CNS relapse which occurred within 12 months after diagnosis of ALL, it was significantly reduced (16.2% vs 6.3%, P<0.05).
Early intensification of intrathecal chemotherapy will reduce the risk of CNS relapse to a very low level in children with ALL securing a higher EFS overall.[18] Some investigators delayed diagnostic L.P. and intrathecal chemotherapy until 1 week after prednisone treatment when circulating blasts are substantially reduced or eliminated in half of the patients.[27] However, 1 week of prednisone treatment may also clear some of blasts from CSF, because steroids can achieve a therapeutic level at the CNS, obscuring application of subsequent risk-directed treatment.[28]
We studied the associated clinical findings at the time of diagnosis of CNS relapse. Headache was the most common presenting symptom (25 patients, 32.8%), followed by facial palsy (21 patients, 27.6%), vomiting (19 patients, 25%) and meningeal irritation signs (13 patients, 17.1%). Accidental discovery of CNS relapse in our patients (i.e., asymptomatic) at time of CNS relapse was reported in 10 patients only, 13.1%. Other studies[30,54]. found most of the patients (75%) were asymptomatic at time of CNS relapse. This difference is mostly due to that in our treatment protocol there is no periodic routine L.P. for diagnosis and therapy during the maintenance phase.
Cranial nerve palsies are rare with the facial nerve being involved most often.[4] It may represent the initial site of relapse in a patient with leukemia.[29] Blurred vision or blindness were the major complaint in 6.5% of CNS-relapsed patients in our study. Isolated optic nerve relapse as the initial site of disease recurrence was diagnosed in few children with ALL by some investigators.[30]
A considerable proportion (30.2%) of our patients who had CNS relapse had developed BM relapse after a short period (median of 3 months). Hematological (BM) relapse remains the major obstacle to long-term disease-free survival.[12] The mean duration between patients who developed BM relapse later on or not were, statistically, not significantly different.
Unfortunately, the mortality rate among our patients was high. Other studies showed better results after CNS relapse. Ribeiro et al[31] reported a 5-years EFS of 70%±11% in patients with isolated CNS relapse after achieving second complete remission, by using an intensive retrieval therapy which was effective and well-tolerated by children with isolated CNS relapse especially those who have not received prior cranial irradiation; most of their patients have no significant neuropsychological impairment. In our country we suffer from lack of the important diagnostic, therapeutic and supportive measures, which might lead directly to these inferior results.
In comparison to patients who are alive, those who died after CNS relapse had shorter duration between diagnosis of ALL and CNS relapse. This indicates a poorer prognosis for ALL patients who developed CNS relapse early. Ritchey et al[32] found that long-term prognosis for children with first complete remission ≥18 months is comparable to that at time of original diagnosis of ALL. While for patients who had CNS relapse within 18 months, the 4-years EFS was 46.2±10%.

CONCLUSION:

Frequency of CNS relapse in ALL patients in our center is much higher than what is reported abroad. But the addition of three intrathecal triple chemotherapy to induction phase decreased it significantly. Further intensification of systemic and CNS-directed therapy is recommended to more decrease of CNS relapse.
Significant risk factors to develop CNS relapse were: male gender, age <2 years at diagnosis of ALL, lymphomatous presentation (massive hepatomegaly, massive splenomegaly, significant lymphadenopathy and mediastinal mass), initial WBC ≥50,000/mm^3 and initial CNS involvement. Prophylactic cranial irradiation was very effective in decreasing frequency of CNS relapse.
Most of CNS relapse patients eventually died, Half of them within 4 months. Patients, who died during the period of the study, had the CNS relapse earlier than the patients who remained alive.

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