A retrospective Study of Testicular Relapse in Acute Lymphoblastic Leukemia

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ABSTRACT:

BACKGROUND:

Testicular relapse in ALL usually appear as painless testicular enlargement mostly unilateral. Diagnosed by wedge biopsy. The testis is a frequent site of relapse.

OBJECTIVE:

To find out the incidence of testicular relapse in ALL, time of diagnosis of testicular relapse, age group more commonly associated with testicular relapse, the association of testicular relapse with other relapses (medullary or extra-medullary), and prognosis of patients with testicular relapse.

PATIENTS AND METHODS:

Aretrospective study in the central teaching hospital of children in Baghdad- unit of hematology and oncology, during January 2000 – December 2006.

Two hundred-four males were studied retrospectively. Informations were obtained from patients' files.

RESULTS:

The incidence of testicular relapse was in 18 patients represented (8.8%) of total cases of boys with ALL below 15 years. Relapse is mainly unilateral in 15 patients (83.3%) and mostly in the right side in 11 patients (61.1%) of total cases with testicular relapse.

There is no significant statistical incidence of relapse with the age of patient represented by 2 cases (6.2%) from (0-2 years), 11 cases (8.2%) from (2-10 years), and 5 cases (13%) more than (10 years). Time of diagnosis of relapse was mainly during the oral maintenance therapy (13) patients (72.5%).

Testicular relapse was isolated in 8 patients (44%) and combined with other relapses in 10 patients (56%) of them 7 patients (39%) with bone marrow relapse and 3 patients (17%) with CNS relapse.

The outcome of patients with testicular relapse was better after discontinuation of chemotherapy "after three years of treatment" (2 cases diagnosed with relapse both of them still alive) represented (100%), while during the maintenance therapy of 13 patients, 6 (46.2%) of them still alive, 6 patients (46.2%) of them died, and 1 patient (7.6%) with no report, while induction chemotherapy 2 cases 1 (50%) alive and 1 (50%) died).

Patients with isolated testicular relapse had better outcome represented by 6 patients (75%) still alive and 2 patients (25%) died, patients with combined relapse had worse outcome, represented by 3 patients (30%) alive, 5 patients (50%) died, and 2 patients (20%) with no report.Incidence of testicular relapse significantly decreased after the introduction of more intensive chemotherapy in Jan 2004 from 9.8% to 3.1%.

CONCLUSION:

Incidence of testicular relapse decrease with introduction of intensive chemotherapy and had higher incidence during the maintenance therapy, associated with increased incidence with other medullary and extra-medullary relapses, and has better prognosis when it is late and isolated than for early and combined relapse.

KEY WORDS: acute lymphoblastic leukemia, testicular relapse.

INTRODUCTION:

Leukemia is a progressive, malignant disease of the blood forming organs, characterized by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. It is classified according to the degree of cell differentiation as acute or chronic and according to predominant type of cell involved as myelogenous or lymphocytic. [1]

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Acute leukemias: are characterized by the presence of "blast", which are immature blood cells. Large quantities of blasts generally overgrow the bone marrow, leaving very little space for normal bone marrow cells. This type generally requires immediate treatment.

Chronic leukemias: are those characterized by large and uncontrolled growth of mature white blood cells. These types of leukemias tend not to progress as rapidly and treatment is often milder than that of acute leukemia. [1]

Testicular relapse in ALL

Usually appears clinically as painless testicular enlargement most often unilateral. The diagnosis must be established by testicular biopsy. When testicular leukemia is suspected clinically, bilateral biopsies are indicated because the disease frequently affect the contralateral testis[2]. Wedge biopsy is the preferred diagnostic technique because this procedure is less likely to result in sampling error.

Before introduction of effective chemotherapy for ALL, clinically evident testicular relapse was a rare event[3]. With improved therapy and prolonged survival, the incidence of testicular involvement increased[4].

Factors that associated with an increased likelihood of developing testicular relapse are:-

High initial WBC count (greater than 20,000/mm^3).

T-cell disease.

Prominent lymphadenopathy and spleenomegaly.

Significant thrombocytopenia (<30,000/mm^3) [5].

The optimal therapy for testicular relapse includes the administration of local radiotherapy and the use of systemic chemotherapy. Radiation dose appear to be a crucial factor in local control. Dose less than 1,200 cGY are generally suboptimal; doses of 2400cGY to both testes have been considered adequate [4,5].

Bilateral testicular radiotherapy is indicated for all patients. Because isolated testicular relapse frequently heralds a systemic relapse, treatment must include intensification of systemic therapy, in addition to bilateral testicular irradiation[6]. Most centers systemically "reinduce" patients who suffer an overt testicular relapse with intensive systemic chemotherapy. This strategy has improved the prognosis for patients with testicular relapse [2].

The prognosis is better if the testicular relapse occur as an isolated event[7]. Isolated testicular relapse is observed more frequently than it is with a concurrent bone marrow relapse although many patients who present with isolated testicular relapse probably have occult intra-abdominal disease [8].

The outcome for patients with an overt testicular relapse vary with the time of presentation. An isolated testicular relapse occurring in a patient on treatment is associated with the worst prognosis [9], in contrast, a late, isolated, overt testicular relapse that occurs off therapy has an even better prognosis [10].

AIM OF STUDY:

To find out the incidence of testicular relapse in ALL timing, the association with other mdullary or extramedullary (CNS) relapses in ALL and prognosis, assess any significant correlation between the incidence of testicular relapse in ALL with age groups of patients having ALL.

PATIENTS AND METHODS:

Between 1st of Jan 2000 through Dec. 2006, , two hundred-four boys, (<15 years) were having ALL, eighteen children of them having testicular relapse, the patients were retrospectively analyzed at central teaching hospital for children, Baghdad, unit of pediatric hematology and oncology.

The diagnosis of ALL was based on morphological features of leukemic cells in bone marrow. informations were obtained from patients' files in the unit of our study regarding age of patient, subtypes of ALL, time of diagnosis of ALL, treatment protocols for patients with ALL before the development of testicular relapse, method of diagnosis of testicular relapse, site of testicular relapse, time of diagnosis of testicular relapse, type of relapse (isolated or combined), and the outcome of patients with testicular relapse, all were reported.

Treatment protocols in this study divided into 2 protocols, the first was used before Jan 2004 which was not specified and include induction therapy of vincristine (1.5 mg/m^2), IV for 4 weeks and prednisolone (40 mg/m^2/day) orally daily for 28 days. L-asparginase was not given during induction because was not available. Bone marrow aspiration was done on day 28 of the induction, after induction the patient was given consolidation cycles of 4 days every two weeks of cytosine arabinoside (100 mg/m^2/day) IV + 6-thioquanine (100 mg/m^2) orally for 4 cycles. CNS prophylaxis therapy was given and consist of 4 doses of weekly intrathecal methotrexate + CNS radiotherapy for patients older than 2 years of

age, then the maintenance therapy is given in from of oral 6-mercaptopurine 75 mg/m^2/day and oral methotrexate 15 mg/m^2/week.

After Jan 2004 more intensive chemotherapy protocol had been used[11] and include induction therapy of vincristine 1.5 mg/m^2 IV weekly for 4 weeks, prednisolone 40 mg/m^2/day orally for 28 days, L-asparginase 10,000 IU/dose start in day 4 for 3 doses a week (IM), adriamycin 30 mg/m^2/dose IV on day 0 and day 14 with intrathecal methotrexate 10-12 mg/m^2, intrathecal cytosine arabinoside 25 mg/m^2, intrathecal hydrocortisone 25 mg/m^2 on days 0, 7, 14. Then start intensification of consolidation with cytosine arabinoside 100 mg/m^2/day for 5 days (IV), etoposide 100 mg/m^2/day for 3 days, L-asparginase 10,000 IU/m^2/day (IM) for 5 days, prednisolone 40 mg/m^2/day orally for 5 days, and vincristine 1.5 mg/m^2 IV one dose given for 2 cycles. Then after intensification patient receive consolidation cycle for 4 cycles every other week of cytosine arabinoside 100 mg/m^2/day IV for 5 days, methotrexate 50 mg/m^2 IV one dose (day0), 6-mercaptopurine 75 mg/m^2/day orally for 5 days, and folinic acid 15 mg/m^2 every 6 hours for 3 days starting on the 2nd day after infusion of methotrexate. Then patient were given CNS prophylaxis of intrathecal triple therapy of methotrexate, cytosine arabinoside, and hydrocortisone weekly for 4 cycles, and radiotherapy for patients older than 2 years. Finally we put them on oral maintenance therapy in the form of oral 6-mercaptopurine 75 mg/m^2/day, and oral methotrexate 20 mg/m^2/week, with intensification cycles every 12 weeks of vincristine 1.5 mg/m^2 IV one dose, prednisolone 40 mg/m^2/day for 5 days, L-asparginase 10,000 IU/m^2/day for 5 days (IM), and cytosine arabinoside 100 mg/m^2/day IV for 5 days. Patients developed testicular relapse usually treated with testicular radiation to both testes with re-induction systemic chemotherapy.

Statistical calculations were performed in our study using chi-square test. P value <0.05 was significant.

RESULTS:

Table 1: Number and percentage of male patients with ALL subtypes by FAB classification.

ALL subtypes	No of patients	Percentage
ALL-L1	83	40.6%
ALL-L2	108	52.9%
ALL-L3	3	1.5%
Undifferentiated ALL	10	5.0%
Total cases	204	100%

ALL-L_2 had more incidence than other subtypes of ALL according to FAB classification.

The incidence of testicular relapse

The total number of patients with testicular relapse after ALL during this period of 5 years is 18 patients which is equal to 8.8% of total cases of boys with ALL.

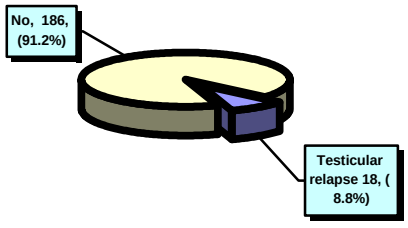

Figure 1: ALL patients with testicular relapse versus no relapse.

Table 2: The occurrence of testicular relapse with ALL in relation to subtype of ALL by FAB classification.

ALL subtypes	No of patients	Patients with testicular relapse*	
		Number	Percentage
ALL-L1	83	9	10.8
ALL-L2	108	9	8.3
ALL-L3	3	-	-
Undifferentiated ALL	10	-	-

*P=0.556; No significant difference

This table shows that there is no significant difference in the incidence of testicular relapse with the subtype of ALL by FAB classification which was 10.8% in ALL-L_1 and 8.3% in ALL-L_2.

Table 3: Incidence of testicular relapse in relation to treatment protocols used for treatment of ALL.

Treatment protocol	No. of patients with ALL	Patient with testicular relapse	
		NO.	Percent
Chemotherapy protocol that used from 2000-2004	172	17	9.8%
Treatment protocol used after Jan 2004-2006	32	1	3.1%

P=0.0033 (significant difference)

The incidence of testicular relapse had been lowered with the introduction of more intensive chemotherapy in Jan 2004 from 9.8% before 2004 to 3.1% after 2004 (till the execution of this study in 2006), this table shows the significant decrease in the incidence of testicular relapse with the introduction of more intensive therapy for ALL.

Site of testicular relapse

The following figure shows that most of cases of testicular relapse unilateral representing (83.3%) while bilateral testicular relapse (16.7%), and mostly in the right testis representing (61.1%).

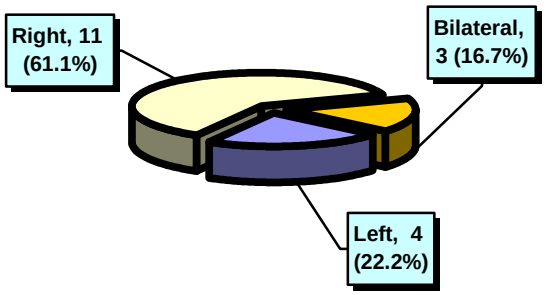

Figure 2: Site of testicular relapse.

Methods of diagnosis of testicular relapse

The following figure shows that 7 (38.9%) of cases of relapse diagnosed by wedge biopsy and

8 (44.4%) of cases diagnosed by FNA, and 3 cases (16.7%) there was no report about the method of diagnosis.

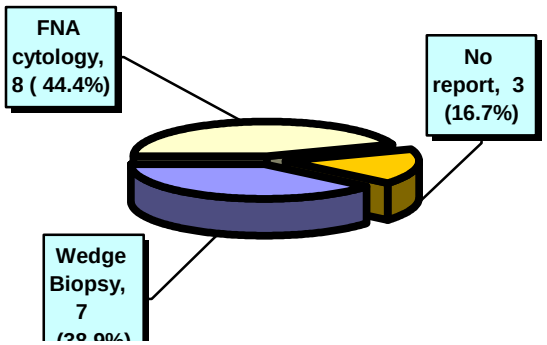

Figure 3: Methods of diagnosis of testicular relapse.

Table 4: Incidence of testicular relapse in relation to age group of patient with ALL.

Age groups (years)	No of patients with ALL	Patients with testicular relapse*	
		Number	Percentage
0-2 years	32	2	6.2
2-10 years	134	11	8.2
> 10 years	38	5	13.1

*P=0.545; No significant difference .

This table shows that there is no significant difference in the incidence of testicular relapse with different age group.

Time of diagnosis of testicular relapse

Most of cases of testicular relapse had been diagnosed during the oral maintenance therapy represented by (13) 72.5%, while at presentation(1) 5.5%, after induction (2) 11%, and after discontinuation of chemotherapy "after three years of treatment" (2) 11%.

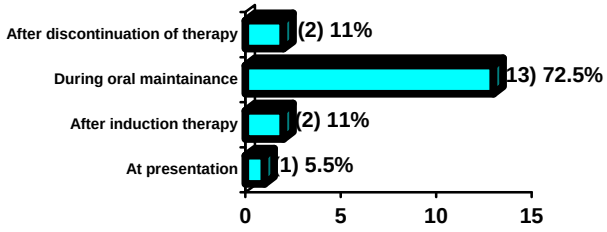

Figure 4: Time of diagnosis of testicular relapse after initial diagnosis of ALL.

Association of testicular relapse with other relapses

the following figure shows that the combined testicular relapse (CNS &/or medullary) occur more commonly than isolated testicular relapse so 10 cases representing 56% were combined, while 8 cases (44%) isolated testicular relapse.

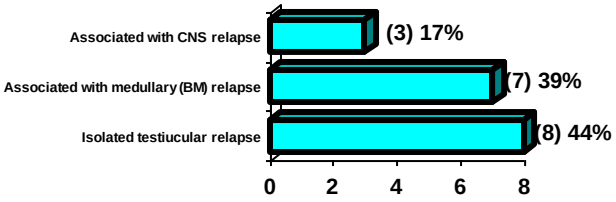

Figure 5: Association of testicular relapse with other medullary or extramedullary (CNS) relapses.

Table 5: Fate of patients with ALL-testicular relapse in relation to time of diagnosis of testicular relapse after diagnosis of ALL.

Time of diagnosis of testicular relapse	No of patients with testicular relapse	No of patients Alive (%)	No of patients died (%)	No of patients with no report; leave treatment (%)
At presentation	1	-	-	1 (100%)
After induction therapy	2	1 (50%)	1 (50%)	-
During oral maintenance	13	6 (46.2%)	6 (46.2%)	1 (7.6%)
After discontinuation of chemotherapy	2	2 (100%)	-	-

The fate of patient with testicular relapse was better when the relapse diagnosed late and after discontinuation of therapy "after three years of treatment" in which we had 2 cases both of them still alive while testicular relapse that present early and during treatment of ALL has poor outcome, as shown in the following table.

Table 6: Fate of patient with ALL testicular relapse in relation to type of relapse.

Type of testicular relapse	No. of patient	No. patient alive (%)	No. of patient died (%)	No. of patient with no report (%)
Isolated testicular relapse	8	6 (75%)	2 (25%)	0 (0%)
Combined testicular relapse (with bone marrow or CNS)	10	3 (30%)	5 (50%)	2 (20%)

The patient with isolated testicular relapse had better outcome so patient who still alive represent 6 (75%) while patient who died were 2 (25%), while in combined testicular relapse (with bone marrow or CNS relapse) the outcome was poor. Patient who still alive represent (3) 30% and who died (5) 50% and in (2) 20% we had no report, as shown in the table above.

DISCUSSION:

Incidence of testicular relapse in ALL in our study was (8.8%) which was similar to previous studies (Baum E, Land V, Joo P, et al) [12] and (Miller DR, Leikin SL, Albo VC, et al) [13] in which the incidence of testicular relapse was approximately (10%) in (Lanskowsky Philip) [14] in which the incidence of testicular relapse occurred in10-23% of boys with ALL.

In this study, with the introduction of more intensive chemotherapy in 2004 the incidence of testicular relapse significantly declined (P=0.0033) from 9.8% on the previous protocol to 3.1%. This is similar to previous studies (Nachman JB, Sather HN, Sensel MG, et al)[15]and (Schrappe M, Reiter A, Ludwig WD, et al)[11] show that the incidence of testicular relapse had declined with the use of more intensive chemotherapy also similar study (Baum E, Heyn R, Nesbit M, et al)[8] shows that the incidence of

testicular relapse had lowered with the use of intensive chemotherapy to less than 5%.

In this study the incidence of testicular relapse had no significant difference with the subtype of ALL according to FAB classification.

In this study most of cases of testicular relapse were unilateral which represented 83.3% while bilateral testicular relapse representing 16.7% there is similar study (Bowman W, Aur R, Hustu H, et al)[2] also shows that testicular relapse in ALL mostly unilateral.

In our study there was no significant difference in the incidence of testicular relapse with ages of patients. A study done by (Ritzen EM)[16] showed that the age over 10 years increase the risk of development of testicular relapse because this age group coinciding with the start pubertal activation.

In this study time of diagnosis of testicular relapse occurred mainly during oral maintenance therapy represented by (72.5%) of the total cases, this differs from (Lanzkowsky Philip) [14] that shows most cases of testicular relapse diagnosed within 2 years of stopping therapy, other studies (Kay HE)[17] and (Givler RL)[18] show that time of diagnosis of testicular relapse ranges from 2 months to several years. In this study combined testicular relapse represented (56%) while isolated testicular relapse represented (44%) of cases. This differs from other study (Baum E, Heyn R, Nesbit M, et al)[8] which showed that isolated testicular relapse occur more often than combined testicular relapse.

In this study the outcome of testicular relapse was better when the relapse was diagnosed after discontinuation of chemotherapy where we had 2 cases of testicular relapse both were still alive, while testicular relapse developed early in the course of ALL had poor outcome. Similar study (Uderzo C, Grazia ZM, Adamoli L, et al)[10] and (Finklestein JZ, Miller DR, Feusuer J, et al)[19] showed that testicular relapse that develop early and during therapy had worst outcome while in late relapse that develop off-therapy had better outcome.

In this study the prognosis of testicular relapse also was better when the relapse was isolated represented by (75%) of patients with isolated relapse still alive, while combined testicular relapse (with CNS or bone marrow) had worst outcome represented by (30%) of patients with combined relapse still alive. Similar studies (Hustu HO, Aur RJ) [7] and (Cap J, Foltinova A, Misikova Z) [20] showed that the outcome was better for isolated testicular relapse and worst for the combined relapse.

CONCLUSION:

The incidence of testicular relapse represented 8.8% of the cases of ALL in the center where our study done. There is no significant correlation between testicular relapse and subtypes of ALL according to FAB classification. The testicular relapse has increased incidence during the maintenance chemotherapy than the other periods after the diagnosis of ALL. Testicular relapse usually associated with increased incidence of medullary (bone marrow) and extra-medullary (CNS) relapses. The prognosis of testicular relapse is better for the late diagnosed relapse than for the early diagnosed and for the isolated than for the combined relapse.

The introduction of more intensive chemotherapy protocols had lowered the incidence of testicular relapse in ALL. There is no significant correlation between the incidence of testicular relapse with the age of patient with ALL.

Recommendation:

We recommend performing bone marrow examination and CSF examination for all children with testicular relapse of ALL to recognize the bone marrow or CNS relapse as testicular relapse may be associated with bone marrow or CNS relapse. Introduction of more intensive chemotherapy to patient with ALL to reduce the incidence of testicular relapse in ALL. Educational programs are mandatory for children with ALL and their families for early recognition of any changes in the testicular size and consistency.

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