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Prognostic Factors Of Adults B-Cell Acute Lymphoblastic Leukemia

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Abstract
Background. B-cell acute lymphoblastic leukemia (B-ALL) is a malignancy of immature B-cell precursors that proliferate in the bone marrow leading to signs and symptoms of bone marrow failure. Clinical, biological and genetic features are having prognostic significance affecting the outcome of those patients. We aimed with this study to analyze the significance of these factors in affecting patients outcome after treatment with complete or incomplete remission.
Patients and methods. This study was carried out on 39 adults B-cell ALL patients who were attending the hematology oncology clinics. All patients were subjected to; History, clinical examination and Laboratory investigations, which included CBC, PB and BM examination, Immunophenotyping and Fluorescence in situ hybridization.
Results. This study was carried out on 39 adult B-cell ALL patients (Follow up was done at day 28 of chemotherapy) show: 16 (41%) patients achieved complete remission (CR) ; while 23 (59%) patients showed incomplete remission (IR). Statistical analysis of patients' outcome with prognostic markers revealed significant association ($p<0.05$) of CR with TLC <50x109/L ($p=0.003$) , age <35 yrs ($p=0.000$) and frequency of t(9;22) with ($p=0.05$).
Conclusion. Age, TLC and t(9;22) are represent the most significant standard prognostic factors in relation to adults B-ALL patients' outcome.

Introduction
Acute lymphoblastic leukemia (ALL) is a hematologic neoplasm produced by impaired differentiation, proliferation and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites**.(1)**

B-cell acute lymphoblastic leukemia (B-ALL) is a malignancy of immature B-cell precursors that mainly affects children younger than 6 years but is also encountered in older children and in adult populations**.(2)**

The age incidence rate is 1.6 per 100,000 individuals per year, with a median age about 14 years. Mainly 60% of the patients are diagnosed before 20years of age. Although survival in adult patients (>19 years old) remains inferior to that achieved for children with ALL**.*(3)***

Patients with B-ALL usually have signs and symptoms of bone marrow (BM) failure, including cytopenias with or without leukocytosis**.(2)**

Many clinical, biological, genetic, and molecular features have been identified as having prognostic significance affecting the outcome of patients with ALL ***(4)***

Patients with ALL are usually treated according to prognostic risk assessment includes clinical features (age and white blood cell [WBC] count at diagnosis), biologic characteristics of the leukemic blasts and response to the induction chemotherapy. Based on these criteria, patients can be effectively stratified into low risk, average or standard risk, high risk, and very high-risk. ***(5).***

Aim of the work

This work aims to detect prognostic factors of B-ALL patients on relation to response to treatment and their affect on the outcome of patients.

Patients and methods

This study was carried out on 39 adults B-cell ALL patients who were attending the hematology oncology clinics. They were 24 males (61.5%) and 15 females (38.5%) with a male to female ratio of 1.6:1 and their age was ranged from 19 year to 71 years.

All patients were subjected to the following: History and clinical examination laying stress on the presence of hepatomegaly, splenomegaly, lymphadenopathy and CNS infelteration. Laboratory investigations, which included: Complete blood count using LH750 (Beckman Coulter), Examination of Leishman stained P.BL. smears. B.M.A and examination of Leishman stained smears. Immunophenotyping on BM or P.BL. samples. Fluorescence in situ hybridization for detection of cytogenetic abnormalities of those cases.

Results

Clinical findings: (Table1).

The current study was carried out on 39 newly diagnosed adult B-cell ALL patients. Out of all patients, 24 (61.5%) were males and 15 (38.5%) were females with male to female ratio of (1.6:1). Their age ranged from 19 to 71 years.

Out of the 39 patients, 19 (48.7%) patients presented with hepatomegaly ., 20 (51.3%) patients presented with splenomegaly., 24 (61.5%) patients presented with lymphadenopathy and 2 (5.1%) patients presented with CNS infiltration.

Laboratory findings: (Table1)

1- Hemoglobin level (Hb): Ranged from 4.6 to 10.1g/dl with a mean value of (7.35±1.6) g/dl. 36 patients (92.3%) had initial hemoglobin level <10g/dl and 3 (7.7%) had hemoglobin level >10g/dl.

2- Total leucocytic count (TLC): Ranged from 2.6 to $101x10^9$/L with a median value of $(51.8±30.2)x10^9$/L. Thirty-five (89.7%) patients presented with leukocytosis with 12 patients (30.7%) of them presented with TLC $>50x10^9$/L. The remaining 4 (10.2%) patients were leucopenic (TLC $<4x10^9$/L).

3- Platelets count: Ranged from 33 to 128x109/L with a mean value of (80.5±26.7)x109/L. Thirty-three (84.6%) patients had platelets count <100x109/L, while 6 patients (15.4%) had platelets count ≥100x109/L.

4- Bone Marrow Examination: According to WHO classification, The absolute BM blast ranged from 24 to $98x10^9$/L with a mean value of $(66±21)x10^9$/L.

5- Immunophenotyping (IPT): The studied 39 ALL patients were expressing CD10.

6- Fluorescence in Situ Hybridization Analysis: Metaphase and/or interphase FISH analysis were successfully performed on 39 BM and/or P.BL. samples and revealed the following: Positive results for t(9;22) was encountered in 11 (28.2%) patients, 11(q23) was detected in 2 (5.1%) patients, t(1;19) was detected in 1 (2.5%) patient.

Follow up & clinical outcome of studied all patients:

Follow up was done at day 28 of chemotherapy. Out of the 39 newly diagnosed patients, 16 (41%) patients achieved complete remission (CR) ; while 23 (59%) patients showed incomplete remission (IR).

Prognostic Markers in Association to Patients Outcome:

Statistical analysis of patients' outcome with prognostic markers revealed significant association ($p<0.05$) of CR with TLC $<50x10^9/L$ ($p=0.003$) , age <35 yrs ($p=0.000$) and frequency of t(9;22) with ($p=0.05$) **(figures 1&2).**

On the other hand, gender, hepatomegaly, splenomegaly, Hb and platlet count showed non-significant statistical difference between the patients who achieved complete remission and those with incomplete remission ($p>0.05$) **(Table 2).**

Table(1): Statistical analysis of clinical and lab data of the 39 newly diagnosed B-ALL patients:

Parameter	No.of patients	Percentage
Gender		
Male	**24**	**61.5%**
Female	**15**	**38.5%**
Hepatomegaly		
Positive	**19**	**48.7%**
Negative	**20**	**51.3%**
Splenomegaly		
Positive	**20**	**51.3%**
Negative	**19**	**48.7%**
Lymphadenopathy		
Positive	**24**	**61.5%**
Negative	**15**	**38.5%**
CNS Infilteration		
Positive	**2**	**5%**
Negative	**37**	**95%**
Hb		
<10g/dl	**36**	**92.3%**
≥10g/dl	**3**	**7.7%**
TLC		
<50x10^9/L	**27**	**69.2%**
≥50x10^9/L	**12**	**30.8%**
Platelet count		
<100x10^9/L	**33**	**84.6%**
≥100x10^9/L	**6**	**15.4%**
Cytogenetic abnormalities		
t(9;22):		
11q(23):	**11**	**28.2%**
t(1;19):	**2**	**5.1%**
Normal karyotypic:	**1**	**2.5%**
	25	**64.2%**
Clinical outcome		
CR	**16**	**41%**
IR	**23**	**59%**

CR: Complete Remission, IR: Incomplete Remission, Hb: hemoglobin, TLC: total leucocytic count.

Table(2): Results of B-ALL patients' outcome in relation to different prognostic factors

Parameter	Groups	No.	%	CR		IR		P	Significance
				No.	%	No.	%		
Age (Years)	≥35 <35	18 21	46.2 53.8	2 14	12.5 87.5	16 7	69.6 30.4	0.000	**HS**
Sex ♂: ♀1.6:1	Male Female	24 15	61.5 38.5	7 9	43.8 56.3	17 6	73.9 26.1	0.057	NS
Hepatomegaly	Yes No	19 20	48.7 51.3	6 10	37.5 62.5	13 10	56.5 43.5	0.242	NS
Splenomegaly	Yes No	20 19	51.3 48.7	6 10	37.5 62.5	14 9	60.9 39.1	0.151	NS
Lymphadenopathy	Yes No	24 15	61.5 38.5	11 5	68.8 31.2	13 10	56.5 43.5	0.440	NS
CNS Infilteration	Yes No	2 37	5.1 94.9	1 15	6.3 93.7	1 22	4.3 95.7	0.791	NS
Hb	<10g/dl ≥10g/dl	36 3	92.3 7.7	16 0	100 0	20 3	87 13	0.133	NS
TLC(x10^9/L)	<50 ≥50	26 13	66.7 33.3	15 1	93.8 6.3	11 12	47.8 52.2	0.003	**HS**
Platelet count(x10^9/L)	<100 ≥100	33 6	84.6 15.4	14 2	87.5 12.5	19 4	82.6 17.4	0.677	NS
Absolute PB Blasts	<4.4 ≥4.4	19 20	48.7 51.3	9 7	56.3 43.8	10 13	43.5 56.5	0.433	NS
t(9;22)	Positive Negative	11 28	28.2 71.8	2 14	12.5 87.2	9 14	39.1 60.9	0.05	**S**

CR: Complete Remission, IR: Incomplete Remission, P: Prevelance HS: Highly Significant, S: Significant, NS: None Significant, Hb: hemoglobin, TLC: total leucocytic count.

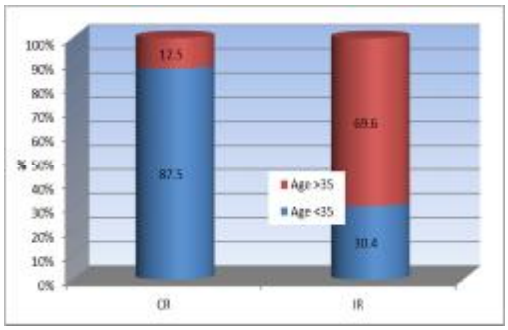

Figure (1): A Bar Chart of Age in relation to B-ALL patients outcome.

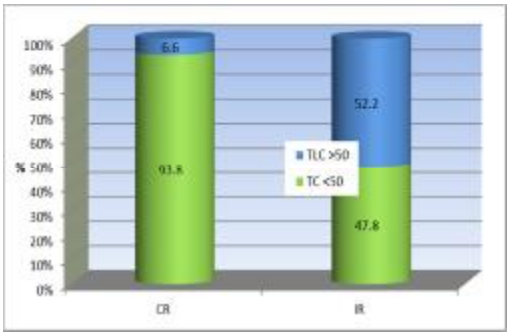

Figure (2): *A Bar Chart of TLC in relation to ALL patients outcome.*

Discussion

This work aims to detect prognostic factors of B-ALL patients on relation to response to treatment and their affect on the outcome of patients.

In our study, we divided the patients according to outcome into complete remission (CR) and incomplete remission (IR). Follow up was done at day 28 of chemotherapy. Out of the 39 newly diagnosed patients, 16 (41%) patients achieved complete remission; while 23 (59%) patients showed incomplete remission.

In the current study, the age of ALL patients ranged from 25 to 71 years with a mean (48 ± 23) years. 21 (53.8%) out of them were less than 35 years old . High significant relation (p=0.000) was detected between the patients ages were less then 35 years and good patients outcome. Similarly to ***(Sallam et al.,2013)*** stated that ALL patients in their study ranged in age from 17 to 74 years with a median age of 52 year**.**

Male to female ratio was (1.6:1) with slight male predominance, Similar observation was reported by ***(Ilana de Franc et al.,2014),***who noticed a male predominance in ALL adults patients. In the present study, no correlation was encountered between gender and outcome (p>0.05). With agreement to; ***(Bassan et al.,2009 and Ilana de Franc et al.,2014)*** recorded no significant difference for gender between patients succeeded to achieve complete remission and those with incomplete remission.

As regards clinical findings in this work, 48.7% of patients had hepatomegaly while 51.3% of patients had splenomegaly, 61.5% of patients had lymphadenopathy and 5% had CNS infilteration . All showed no significant association (p>0.05) with patients outcome is in concordance with ***.(Ustwani Omar et al.,2016).***

As regards the haematological findings, the initial TLC, four (10.3%) patients were leucopenic, while all the rest; thirty-nine (89.7%) presented with total leucocytosis, 13 (33.3%) out of them were $\geq 50X10^9$/L. High significant relation (p=0.003) was detected between the initial TLC $\geq 50X10^9$/L and poor patients outcome. These results show agreement with ***(Paul Shilpa et al., 2016).*** All patients were anemic and thrombocytopenic. There is no significant statistical relation was detected between Hb level<10g/dl (p=0.133) and platelets $<100x10^9$/L (p=0.677) and patients outcome.

There was high significant, negative correlation between outcome and positive philidelphia chromosome t(9;22). among 11 cases with ph +ve only two cases had CR but nine cases had IR. these results are in agreement with those reported by ***(Aldoss et al.,2015).***

Conclusion

Age, TLC and t(9;22) serve as a powerful prognostic marker in adulthood B-ALL. They represent the most significant standard prognostic factors in relation to patients' outcome.

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