Original Articles

Outcome of Adult Acute Lymphoblastic Leukemia: a Single Center Experience

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Introduction

Acute lymphoblastic leukemia (ALL) in adults is a rare malignancy. It represents 1-2% of all cancers1, however it accounts for 20% of adult leukemias. Adult ALL is a heterogeneous disease significantly different from childhood ALL. There are marked differences both in terms of biological factors and clinical outcomes.2 The complete remission rates with induction therapy program in adult ALL ranges from 60-90% but the 5-year disease free survival is only 25-35%. This is in contrast to childhood ALL in which the complete remission rates and overall survival are about 80%.In adults poor outcome is associated with older age, high white cell count and Philadelphia chromosome positivity.3-7

There are a number of studies about the outcomes of adults diagnosed to have ALL in the literature. However, such information is sparse from our part of the world. This study was designed to describe the survival outcomes of adult patients with ALL seen in a Pakistani population.

Patients and Methods

Study design

This was a retrospective study conducted at the Aga Khan University Hospital on consecutive adult patients (more than 14 years of age) diagnosed to have ALL between January 1992 and December 2000.These patients were followed up till December 2001.

Data collection procedure

The medical record department of the hospital retrieved the medical records of patients. The department has a computerized database and uses ICD-9 (International Classification of Disease, 9th edition).8 The data of all patients were analyzed with respect to clinical presentation, morphological and immunopathological features and treatment outcomes.

Inclusion criteria

Consecutive patients diagnosed to have ALL were included in the study according to the FAB (French American British) classification.9 Immunophenotyping was carried out in all cases. Flowcytometric analysis was only available after 1995 and hence immunophenotyping was performed in 42 out of 58 patients using FACScan (Becton Dickinson, USA). The following monoclonal antibodies were used: T lineage associated antigens: CD3, CD5, CD7 B lineage antigens: CD19, CD20, CD22 and non-lineage restricted antigen CD10. Cytogenetic studies were started in 1996 and were performed in 19 patients. Cerebrospinal fluid examination to document CNS involvement was done in all patients.

Exclusion Criteria

Those patients who were diagnosed to have acute lymphoblastic leukemia L3 (FAB type) and chronic myeloid leukemia transformed to acute lymphoblastic leukemia were excluded.

Treatment

Pretreatment investigations included complete blood counts, blood chemistry including liver, renal function tests, LDH, uric acid and serum electrolytes. Patients were treated using Medical Research Council United Kingdom ALL (MRCUKALL X AND X11) protocols. Twelve and 46 patients received treatment according to the MRCUKALL X and MRCUKALL X11 protocols respectively.

Statistical Methods

The data were collected on a computerized database and were analyzed on SPSS for Window's version 10.0. Numerical variables were compared using student's t-test and qualitative variables were compared using chi-square and Fischer's exact test. Kaplan - Meier curves was used to calculate survival outcomes and Cox - proportional hazard model for multivariate analysis.

Results

During the study period, 68 patients were admitted with a diagnosis of ALL. Ten patients left the hospital after the diagnosis to receive treatment elsewhere. A total of 58 patients were therefore evaluable for this study.

Details of clinicopathological features for all 58 patients are shown in Table 1. Mean age was 25.1±12 years. Median age was 20 years (range 15 to 60 years) and 45 (77.5%) patients were <30 years of age. There were 45 males and 13 females.

The poor prognostic factors according to Luken's criteria[10] were male gender 45 (77.5%), white cell count more than 50x109/L, 18 (31%), splenomegaly 37 (62.7%), LDH more than 1000 i.u/L 44(75.8%) and L2 morphology 37 (62.7%).

All 58 patients received treatment and were evaluable for response. Out of these 58 patients, 12 received treatment according to UKALL X protocol, whereas, UKALL XII protocol was administered to 46 patients. Overall 42(72.4%) patients went into complete remission. Seven (58%) patients on UKALL X and 35 (74%) on UKALL XII acquired complete remission. Median time to achieve complete remission was 30 days (range 20-43 days).

Thirteen patients died during induction chemotherapy. The primary cause of death was sepsis (n=10) and progressive disease (n=3). Three patients died while on reintensification after remission secondary to sepsis.

After a median follow up of 9 months (1.0-116), 11(18.9%) relapsed with systemic disease and died whereas 18 (31%) patients were alive and in complete remission at the end of study period.

Survival Outcomes

The Kaplan and Meier survival curves revealed a 5-years probability of survival of 42%. The median survival for the entire group was 18.6 months (Figure 1).

Five-year probable disease free survival was 44% with median disease free survival for the entire group being 18 months (figure 2). Univariate analysis showed that age more than 30 years, male gender, white cell count more than 50x10 9/L and hemoglobin more than 10gm/dl were risk factors for poor outcome. Multivariate analysis revealed that age more than 30 years (p valve <0.05), male

sex (p valve <0.01) and higher white cell count (p valve <0.01) were independent risk factors for poor survival. Based on three clinical risk factors, three groups of patients were identified (Figure 3).

With no risk factor (n=9), or one risk factor (n=27), the probability of 5 year overall survival was 75% and 54% respectively. However, the survival was only 22% in those patients who had two or three risk factors (n=22).

Discussion

Acute lymphoblastic leukemia is a disease with marked difference in the survival outcomes between adults and childhood disease.[11] In this retrospective study we have observed three important prognostic factors i.e. age more than 30 years (p value <0.05), male gender (p value <0.01), and high white cell count (p value <0.01). All these factors are already established as indicators of poor outcome[12,13] and our study confirms their relevance to our population as well.

The mean age was 25 years compared to more than 30 years as noted in several Western studies.[3,11,14] Several studies demonstrate that increased age is associated with shorter remission and results in decreased survival. Patients more than 35 years had a poor outcome, even for those who received the complete treatment indicating that advance age is an independent risk factor in adult ALL.[6]

There was a definite male preponderance similar to that reported in Western literature.[10,15-17]

Apart from age and gender, high white cell count at presentation also influenced the achievement of complete remission negatively in adult ALL in our study.

Positive Philadelphia chromosome is an important poor prognostic factor[18,19], however, karyotyping was introduced late at our center and the numbers of cytogenetic results are too few to assess an impact on the overall outcome.

Median survival of 18.6 months and 5-year probability of overall survival of 42% is comparable to those reported in other studies[6,14,20] Majority of our patients belonged to middle to lower socioeconomic group and hence under-nutrition was common. This could well be the reason[21] for the substantial number of deaths during induction in MRC UKXII protocol, which is an intensive and substantially toxic protocol.

These findings would help physicians to risk stratify the patients into low risk and high risk groups. The 5-years probability of survival of 75% in low risk patients (no risk factor) is promising, and thus their treatment protocol in the subsequent studies may require only minor alterations. On the other hand, for high risk patients (2 or 3 risk factors), with 5-years probability of survival of 22%, a further intensification of chemotherapy is warranted .They may alternatively be offered the option of allogenic bone marrow transplantation in first remission, if an HLA matched donor is available.

Conclusion

We conclude that three factors influence the survival outcomes in adult lymphoblastic leukemia. They are more than 30 years of age, male gender and white cell count more than 50 x 109/L at presentation. Studies from other centers however would help in further establishing the prognostic factors in this group of patients.

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