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Clinical Features and Treatment Tactics of Acute Lymphoblastic Leukemia in Adolescent Children

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Abstract: This article reviews a survey that included 296 diagnosed cases of acute lymphoblastic leukemia over the age of 12 years. The diagnosis of ALL was made based on bone marrow aspiration, biopsy, flow cytometry, and cytogenetics. In this study, complete remission was observed in 90.9% of cases. The treatment-related mortality rate in our study was 15.3%.

Keywords: Acute lymphoblastic leukemia (ALL), treatment related mortality, remission induction, Philadelphia chromosome.

Introduction. Acute lymphoblastic leukemia is a malignant disease classified on the basis of B cell versus T cell lineage. More than two thirds of cases of ALL are B cell phenotype. B cell ALL is primarily a disease of children less than 6 years old and second peak in adults more than 60 years. T cell ALL presents in late childhood and adolescents. Both B and T cell ALL occur more frequently in males than females. The cause of ALL is unknown but it may be associated with ionizing radiation and unidentified infectious agents.

According to WHO, the presence of >20% blast cells in bone marrow is the diagnostic criteria of ALL. Identification of ALL sub types based on immunophenotyping, cytogenetic and molecular markers has resulted in inclusion of Philadelphia like ALL and T cell precursor ALL that affect the prognosis of disease. The identification of the Philadelphia (Ph) chromosome warrants the addition of tyrosine kinase inhibitors (TKI) to the chemotherapy. The remission induction for ALL is inspired by pediatric protocols including multi-agent chemotherapy regimens. With induction therapy, complete remission rates are very high, accounting for 60-90%; however, 5-year disease-free survival is not the same, and it is merely 25-30%.

Objective. To determine the treatment related mortality in adolescents and young adults of acute lymphoblastic leukemia in a resource limited setup at Samarkand.

Materials and methods: An observational study was conducted at the Department of Medical Oncology, Samarkand State Medical University, Uzbekistan, which included 296 diagnosed cases of acute lymphoblastic leukemia more than 12 years of age. Patient's record was reviewed for age, gender, address, complete blood count, percentage of blast, chemistry, hepatitis B surface antigen and anti-HCV antibodies at the time of presentation.

The diagnosis of ALL was established based on bone marrow aspiration, biopsy, flow cytometry and cytogenetics. A repeat bone marrow biopsy was performed on the 28th day of remission induction. Complete remission was defined as the presence of <5% blasts, partial remission as 5-19% blasts and refractory disease as >20% blasts.

Data: A total of 296 cases were reviewed for age, gender, address, HBV/HCV status, flow cytometry report, peripheral film, gene markers, cytogenetics, bone marrow examination and

outcome. Majority of the patients were male and from 19 – 40 years age group with a median age of 22 years. Males were more affected than females 202(68.2%) vs 94(31.8%). More cases, 150(50.7%) were reported in the 19-40 years of age group, followed by 110(37.2%) in (12-18y), 25(8.4%) in (41-60y) and 11(3.7%) in patients greater than 60years of age with a median age of 22. BCR-ABL was done in 111(37.5%) of patients and resulted positive in 20(6.8%). Of 296 patients, 21 (7.1%) did not follow up. 275 patients received induction chemotherapy; All BCR-ABL-positive patients received tyrosine kinase inhibitors. 42 patients died during the first chemotherapy induction resulting in a TRM of 15.3%, and 14 (5.1%) left against medical advice. 219 patients were discharged. Among them, complete remission was observed in 199(90.9%) of the cases, 9(4.1%) in partial remission and 11(5%) showed refractory disease.

Results. A total of 296 patients of ALL and lymphoblastic lymphoma above 12 years of age were included in the study. The overall median age was 22 years. Most cases 150(50.7%), were observed in the age group of 19-40y, followed by 110(37.2%) and 25(8.4%) in the age group of 12-18y and 41-60y, respectively. The lowest number of cases, i.e., 11 (3.7%) were seen in patients above 60 years of age. There was significant male predominance with a male to female ratio of 2.1:1. Of these cases, 202 (68.2%) were males, and 94 (31.8%) were females.

In 110 patients with ALL, 120 port-a-catheters were placed. Three days before the catheter was inserted, most patients began their chemotherapy. The infection rate was 0.35/1000 catheter days, and there were 16 catheter-associated infections in total (13.33%). The risk of catheter-associated infection in children with severe neutropenia on the day of insertion (n = 59) was 15.29%, compared to a rate of 22.46% in children who were not severely neutropenic (500 cells/mm3). 10 (8.35%) of the 120 port-a-catheters had to be removed owing to infection.

Out of 296 patients 206(69.6%) of the cases had more than 20% blast cells, 47(15.9%) had 5-19% blasts and 37(12.5%) had blast percentage less than 5, on peripheral film. The available data showed positive HbsAg in 7 out of 155 patients, whereas only 2 had anti HCV antibodies out of 153. Out of 296 cases BCR-ABL was performed in 111(37.5%) cases, and it was detected in 20(6.8%) patients.

Out of 296 patients 21 (7.1%) did not follow up at our setup. 275 patients received remission induction chemotherapy, 231 (85.5%) patients received CALGB 8811, 26(9.62%) received CALGB 10403, 6(2.2%) HCVAD/Ara-M and 12(4.4%) VCR-Steroids.

All BCR-ABL-positive patients received tyrosine kinase inhibitors; Imatinib 600mg per day. Out of 275, 42 patients died during the remission - induction resulting in treatment related mortality (TRM) of 15.3%, and 14 (5.1%) left against medical advice. 219 patients were discharged. Among them, complete remission was observed in 199(90.9%) of the cases, 9(4.1%) in partial remission and 11(5%) showed refractory disease.

Complications: Acute lymphoblastic leukemia most commonly cause alterations in WT1, NOTCH1, EZH2, BCORL1, and USP7.

Discussion: Due to non-availability of tumor registry in Uzbekistan the exact incidence of ALL (Acute Lymphoblastic Leukemia) in various population groups is not known. The majority of reports of survival outcomes for ALL have particularly emphasized long term mortality from developed countries. The information about treatment related mortality in resource limited countries is scarce. The lack of availability of advanced molecular testing and infrastructure for supportive measures during remission induction leads to higher treatment related mortality in our setup. This study is a retrospective observational study mainly focused on determining demographics and clinical outcomes at a resource limited setup in Samarkand, Uzbekistan.

The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and second peak around the 50 years of age8 Our study showed peak incidence in patients between 19-40 years and median age of 22 years. Another publication of the limited number of patients from our country also showed a median age of 18 years. Whereas in another study the

median age was 28 years. The difference in age at presentation in various regions may be due to geographic and ethnic influence.

Acute lymphoblastic leukemia was diagnosed predominantly in males in our study with a male to female ratio of 2.1:1. Various studies also shows higher percentage of males suffering from ALL (Acute Lymphoblastic Leukemia). Philadelphia chromosome positive ALL is clinically distinct variant of ALL. In our study PCR BCR-ABL reports of only 111(37.5%) patients were available in record and it was positive in 20(6.8%) patients, so it is difficult to compare the results with the world-wide or local data.

The treatment related mortality 15.3% in our study. Different studies across the world showed much lower treatment related mortality i.e., 9% and 4.6%. Whereas another publication from resource limited setup showed the induction related mortality of 12% that is almost comparable to our data. Research and better health-care facilities have significantly improved outcomes in developed countries. Challenges for treatment in developing countries are socio-economic factors, delayed presentation, higher disease burden, resistant infections, lack of supportive services and intensive care facilities.

In our study, complete remission was observed in 90.9% of the cases. These results were comparable with the data found worldwide.

Due to lack of education and public awareness, patients usually present late with advanced disease. Access to specialized cancer treatment centers, support services and trained healthcare professionals is difficult due to limited resources in low-income countries. Many patients cannot afford costly and prolonged courses of treatment. Moreover, differences in patient population and treatment regimens may also contribute to inconsistency in results.

The current study has some limitations. These results may not reflect treatment outcomes across the country.

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