TREATMENT RELATED MORTALITY IN ADOLESCENTS AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Key words: 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%.

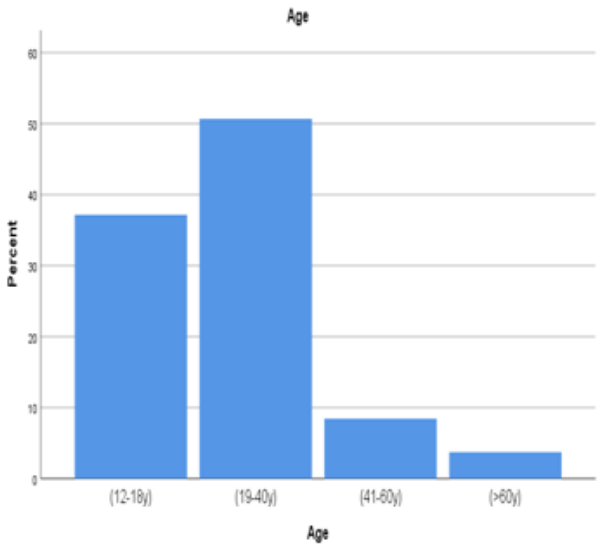
Objective: To determine the treatment related mortality in adolescents and young adults of acute lymphoblastic leukemia in a resource limited setup at Samarkand.

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 on the basis of bone marrow aspiration, biopsy, flow cytometry and cytogenetics. The chemotherapy regimens used in our study for the remission induction were CALGB-8811, Hyper CVAD and CALGB-10403 for healthy young patients. Vincristine and

steroids for elderly patients with comorbidities and poor performance status. Tyrosine kinase inhibitors – Imatinib was added to all Philadelphia positive patients in addition to remission induction chemotherapy. 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. The majority of 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.



Baseline hemoglobin, white blood cells and platelet count are given in tables A, B and C respectively.

Table A

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<8	153	51.7	51.7	51.7
	8-10	94	31.8	31.8	83.4
	>10	48	16.2	16.2	99.7
	4	1	.3	.3	100.0
	Total	296	100.0	100.0	

Table B

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<10000	120	40.5	40.5	40.5
	10000-50000	88	29.7	29.7	70.3
	50000-100000	37	12.5	12.5	82.8
	>100000	51	17.2	17.2	100.0
	Total	296	100.0	100.0	

Table C

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<10000	30	10.1	10.1	10.1
	10000-100000	210	70.9	70.9	81.1
	>1000000	56	18.9	18.9	100.0
	Total	296	100.0	100.0	

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.

Discussion: Due to non-availability of tumor registry in Uzbekistan the exact incidence of ALL in various population groups is not known. Most 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. Another publication of the limited number of patients from our country also showed the 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. 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 in developed countries.

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

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