ORIGINAL ARTICLE

# Remission Rate of Acute Lymphoblastic Leukemia (ALL) in Adolescents and Young Adults (AYA)

Anita Vallacha, Ghulam Haider, Wiky Raja and Dinesh Kumar

## Abstract

**Objective:** To determine the remission rate in adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL).

**Study Design:** Descriptive study.

**Place and Duration of Study:** Department of Oncology, Jinnah Postgraduate Medical Centre (JPMC), Karachi from January, 2016 to March, 2017.

**Methodology:** Adolescent and young adult (AYA) patients aged 15-39 years, newly diagnosed with acute lymphoblastic leukemia from January, 2016 to March, 2017. Diagnosis was confirmed by bone marrow trephine biopsy and immuno-phenotyping. All the patients were treated with daunorubicin, vincristine, prednisone, and L-asparaginase in the induction phase. The response evaluation was done on day 35 of the induction phase and the remission rate was assessed by the bone marrow examination.

**Results:** Of the total 50 AYA patients diagnosed with ALL, 41 patients could complete induction phase and 9 patients died during the first week of induction, therefore excluded from the study. Forty (97.8%) patients were <35years of age, 28 (68.3%) were male, of female 10 (24.4%) were housewives, 33 (80.5%) patients belonged to Sindh, 28 (68.3%) presented with fever and body ache, 17 (41.5%) patients had precursor B cell type ALL, with 7 (17.1%) patients had hemoglobin of <7 g/dL,11 (26.8%) patients had white cell count of >30x10$^9$/L, platelet count of <20x103/µL in 6 (14.6%) patients and complete morphological remission was reported in 29 (70.7%) patients.

**Conclusion:** The remission induction rate was 70.7% in the adolescents and young adults with acute lymphoblastic leukemia at the study centre.

**Key Words:** *Remission. Acute lymphoblastic leukemia. Adolescents. Young adults.*

## INTRODUCTION

Acute lymphoblastic leukemia is a heterogeneous group of hematological disorder and the most common pediatric cancer that is characterized by the abnormal proliferation of immature cells of lymphoid lineage in the bone marrow, peripheral blood, and other organs.[1] The peak incidence of acute lymphoblastic leukemia is seen at 2-10 years of age. The annual incidence of this cancer in Pakistan is unknown. The annual incidence reported from other countries is 30-40 per million children of less than 18 years of age.[2] Acute lymphoblastic leukemia represents 20% of all leukemias among the adults. Its annual incidence is about 1.58 per 100,000 individuals per year in the age adjusted adults in United States with 6,590 new cases and 1,430 deaths in 2016.[3]

There are no uniform age subgroups of acute lymphoblastic leukemia defined. Age of the patients with pediatric ALL ranges from 0-14 years, adolescents from 15-19 years, young adults from 20-39 years, adults from 40-60 years, and older adults and elderly patients >65 years.[4] Thus, adolescent and young adult (AYA) patients include the age group of 15-39 years. AYA are defined as a vulnerable population by National Cancer Institute.[5] Several clinical trials have shown disappointing results in adults as compared to children with cure rate of 90% and 30-40%, respectively.

Various socioeconomic factors, such as lack of clinical trials, lower compliance rates, and long delays in the initiation of the treatment, may result in the poor outcomes in the AYA population.[6] Children with ALL are treated successfully, but prognosis deteriorates markedly with the onset of adolescence to adulthood. This can be estimated by higher relapse rates and shorter survival in AYA population.[7] There are three subtypes of acute lymphoblastic leukemia with variation in the prevalence, which depends on the environmental, geographical, socio-economic, ethnic and racial factors. These include B cell lineage (precursor B cell ALL, and mature B cell ALL) and T cell ALL with prevalence of 75% and 25%, respectively. Several prognostic factors predict the complete morphological remission rate. These include clinical and laboratory factors like age, sex, white cell count, and good cytogenetics.[8] There is no standard protocol defined in AYA patients with ALL. These patients are treated either with pediatric protocol or with an adult protocol, depending on the treating physician's choice. Clinical trial is recommended in the first line of treatment.[3]

*Department of Oncology, Jinnah Postgraduate Medical Center (JPMC), Karachi.*

*Correspondence: Dr. Anita Vallacha, Resident, Department of Oncology, Jinnah Postgraduate Medical Center (JPMC), Karachi.*
*E-mail: anita_vallacha@hotmail.com*

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In Pakistan, the demographics and the outcome of AYA with ALL is not known. This study aimed to determine the remission rate after induction chemotherapy in AYA patients with ALL. This study will hopefully make platform for further multicenter studies and help in improving treatment options, and thus the outcome.

## METHODOLOGY

Patients of age 15-39 years (AYA) with diagnosis of ALL presented to the Oncology Department, Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January 2016 to March 2017 were included in the study. The data was prospectively collected with a sample of 50 patients. Patients with newly diagnosed ALL, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, either gender and ejection fraction >55%, were included; patients with central nervous system (CNS) infiltration, ECOG performance status >2 and Philadelphia positive on cytogenetic studies, were excluded. Enrollment of the patients started after the ethical review committee approval from JPMC. Written informed consent was taken. A proforma was structured for this study.

Peripheral blood and bone marrow samples were taken from all the patients before the treatment. Diagnosis of ALL was made on the basis of >20% lymphoblast in bone marrow on morphological and immunohisto-chemical studies, immunophenotyping were performed where morphology and immunohistochemistry was inconclusive. Also cytogenetic studies were done to rule out Philadelphia positive ALL. The clinical variables observed were age at diagnosis, gender, clinical features at presentation, and the laboratory variables were subtype of ALL, hemoglobin, white blood count and platelet count. Echocardiography of all patients was done before starting the treatment.

The treatment protocol was based on DVP-Asp (Linkers regimen) with some modifications due to logistic reasons.[9] The chemotherapy administered includes daunorubicin, vincristine, prednisone and L-asparaginase (Table I). We could not assess initial treatment response on day 14 as given in protocol, because of lack of facilities of bone marrow trephine biopsy in our hospital setup and sickness of patients due to febrile neutropenia as these factors could not allow patients to move to other hospital laboratories for bone marrow trephine biopsy for initial response evaluation. Therefore, treatment response was evaluated by bone marrow analysis on day 35 of the induction, as almost all patients had become stable by that time. Complete morphological remission (CR) was defined as <5% blasts in the bone marrow, no leukemic cells in the peripheral blood, absolute neutrophil count of at least $1.0x10^9$/L, and platelet count of at least 100x103/μL, and the absence of extramedullary leukemic blasts.

**Table I:** Remission induction therapy.

| | |
|---|---|
| Daunorubicin | 50mg/m2 IV, days 1-3 |
| Vincristine | 2mg IV, days 1, 8, 15, 22 |
| Prednisone | 60mg/m2 PO, days 1-28 |
| L-Asparginase | 6000 u/m2 IM, days 17-28 |

*IV = Intravenous; PO = Per oral; IM = Intramuscular*

Statistical analysis was done by using SPSS version 17.0. For patients' characteristics, descriptive statistics were used. Frequencies with percentages were calculated for categorical data.

## RESULTS

A total of 50 patients with Philadelphia negative ALL were included in the study. Of them, 41 patients had completed induction phase. Nine patients died during the first week of induction because of infection and progressive disease, and could not complete induction phase of treatment. Therefore, they were excluded from the study and remission rate of 41 eligible patients were reported, who had successfully completed the induction phase of treatment.

All the patients (n=41) were between 15-39 years of age, from which 21 (51.2%) were 15-20 years, 8 (19.5%) were 21-25 years, 5 (12.2%) were 26-30 years, 6 (14.6%) were 31-35 years, and 1 (2.4%) was 36-39 years. There were 28 (68.3%) males and 13 (31.7%) females. Among the female patients, 10 (24.4%) were housewives. Out of the total population, 11 (26.8%) were students, 8 (19.5%) were farmers, and 12 (29.3%) belonged to other professions. Thirty-three (80.5%) participants belonged to province of Sindh, seven (17.1%) to Balochistan, and 1 (2.4%) to Khyber Pakhtunkhwa (KPK). Fever and body ache (n=28; 68.3%) were the most common presentation followed by fever and weight loss in 7 (17.1%) patients. Four (9.8%) patients had presented with fever and bleeding, one patient (2.4%) with bleeding and one (2.4%) with weight loss alone. Immunophenotyping results at diagnosis were available for 27 (65.9%) patients. Of them, 17 (41.5%) cases were classified as having Precursor B-cell ALL, 6 (14.6%) as B-cell ALL, and 4 (9.8%) as T-cell ALL. Fourteen patients (34.1%) were with only diagnosis of acute lymphoblastic leukemia with no subtype defined.

Thirty (73.2%) patients had white cell count of $<30x10^9$/L, while 11 (26.8%) patients had $>30x10^9$/L. Of them, 6 (14.6%) patients had white cell count $>100x10^9$/L. Nineteen patients (46.3%) had hemoglobin between 7-10g/dL, while 15 (36.6%) patients had above 10g/dL, and 7 (17.1%) patients had below 7g/dL. In majority of patients (n=17, 41.5%), platelet count were in the range of 20-$50x10^3$/μL, while 6 (14.6%) had below $20x10^3$/μL, and 8 (19.5%) had above $50x10^3$/μL. Ten patients (24.4%) had platelet count of $>100x10^3$/μL. All the patients were given four drugs as per Linker's ALL

protocol (Table-I). Bone marrow analysis for response evaluation was done on day 35 of the induction. Complete remission rate was achieved in 29 (70.7%) patients, while 12 (29.3%) patients had not achieved morphological remission.

## DISCUSSION

Due to lack of population based tumor registry in Pakistan, the exact incidence of ALL in AYA population is not known. The incidence rate (age adjusted) of ALL in U.S population is 1.7 per 100,000 individuals per year,[10] with approximately 5,970 new cases and 1,440 deaths estimated in 2017.[11] The median age at diagnosis is 15 years with 56.1% patients diagnosed below 20 years of age.[12] Little or none has been published on the remission rate of ALL in AYA population in Pakistan. The National Cancer Institute has defined population of 15-39 years of age as AYA population. These patients have different characteristics as compared to children and older adults. These characteristics could be disease-related (biology and clinical presentation) or patient related (treatment tolerance and psychosocial aspects). In comparison to children (1-9 years), AYA patients with acute lymphoblastic leukemia have higher relapse rates and shorter survival.[13]

This study was done to look for the complete remission rate of AYA patients with ALL at the study centre, i.e. Jinnah Postgraduate Medical Centre, Karachi. Good clinical prognostic factors for remission induction are age <35 years, male gender, low white cell count $<30x10^9$/dL and good cytogenetic.[14] In this study, majority of patients (n=40, 97.8%) were <35 years of age. In this study, male predominance (68.3%) was reported. In adult patients with ALL, about 75% of cases comprised of B-cell lineage subtype and 25% of T-cell lineage.[15,16] In 65.9% patients of this study, ALL subtype was defined, which includes 56.1% of B-cell lineage and 9.8% of T-cell lineage. In 34.1% patients, subtype of ALL was not defined. This may be due to loss of differentiation on immunophenotyping because of advanced disease, but further studies are required for this different behavior of leukemic cell. In 11 (26.8%) patients, high white cell count $>30x10^9$/dL was documented at the time of presentation. High white cell count ($>30x10^9$/dL) remained an unfavorable prognostic marker and associated with decreased remission rate.[14,17] These patients required aggressive supportive management because of higher risk for developing tumor lysis syndrome and other complications. In 14.6% patients, platelet count were found <20x103/µL, but no life-threatening bleeding was reported.

For AYA patients with ALL, there is no single standard treatment regimen developed. They are either treated with pediatric protocol or with an adult protocol. Treatment protocols given are based on physician's preference and institutional practice. Multiple clinical trials had reported disappointing results in adults with cure rates of 30-40%; whereas in children, with cure rate of 90%. Five-year event-free survival rate for AYA patients with ALL, treated with adult and pediatric protocol, ranges from 34% to 69% and 63% to 74%, respectively.[18-20] The National Comprehensive Cancer Network guidelines currently recommends a clinical trial in newly diagnosed ALL in AYA patients instead of any standard regimen as first line treatment. The primary goal of induction is to achieve complete clearance of blasts and normalization of peripheral blood count. With either of pediatric or adult protocol, the complete remission rate reported is approximately 90%. Some multi-center trials had reported CR rates as 93.5% for GRA ALL 2003, 94% for DFCI consortium, 90% for CCG 1882, and 98% for PETHEMA ALL-96.[19,21-23]

In this study, the complete remission rate CR achieved was 70.7% at the end of the induction. Other multicentre trials had also reported lower CR rates: 64% for the ECOG trial3, 68% for the SWOG trial, 74% for the GMALL-01 (German ALL trail), and 75% for the GMALL-02 trial.[24] Therefore, we need more aggressive and modified regimen to improve the complete remission rate and thus the overall survival.

This is a single-center study with a small number of patients as compared to others. The estimated complete remission rate in this study is inferior as compared to other studies. Therefore, more multicentre studies are needed to identify other risk factors behind the poor outcome. The authors have reported the initial response to therapy, but further follow-up studies are required to evaluate the overall survival. This is the only study so far published from Pakistan. During the induction phase, high rates of toxic deaths were noted secondary to infections. Therefore, aggressive management of febrile neutropenia is needed. This study emphasizes designing of more aggressive treatment for AYA patients with ALL.

## CONCLUSION

Remission induction rate was 70.7% at the study centre in the adolescents and young adults with acute lymphoblastic leukemia.

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