Mortality Analysis in Children during Induction Therapy for Acute Lymphoblastic Leukemia

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ABSTRACT

Objective: To find out the death rate and analyze the causes of death in children with Acute Lymphoblastic Leukemia (ALL) during induction chemotherapy.

Patients & Methods: This cross-sectional study was conducted at Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad. All children ranging from 1-13 years of age, and diagnosed as ALL, registered at Children Hospital PIMS, from January 2014 to September 2015 were included in the study. All patients were treated with the BFM protocol. Mortality data during induction therapy was collected and analyzed including rate and cause of death.

Results: Out of 48 newly diagnosed cases of ALL, 10 (20.8%) patients died during induction phase. So, the induction death rate in the study period was 20.8 %. Bleeding was observed in 5 (50%) patients and was thus the commonest cause of death, followed by sepsis which was observed in 4 (40%) patients. Tumor lysis syndrome was observed in 1 (10%) patient. CNS was the major site of bleeding.

Conclusion: The death rate during induction therapy is high in our setup. The major cause of death in the present study was bleeding, followed by sepsis. High death rate in our study was attributed to failure to arrange platelet and blood transfusions, and increased rate of infections particularly in low income families. It is emphasized that supportive therapy in the form of platelets and blood transfusions should be given on urgent basis to the children who present with low platelet counts. A good antibiotic cover should be given to treat infections and most important aspect is that patient’s caretaker’s education regarding the patient care is ensured.

Keywords: Acute lymphoblastic leukemia, Bleeding, Induction therapy, Infection, Mortality.

Introduction

Acute Lymphoblastic Leukemia (ALL) is a malignant disorder that results from the abnormal proliferation of the immature cells of the lymphoid lineage in the bone marrow.1

ALL is the most common malignancy in children.1-4 It accounts for about 75-80% of cases of childhood leukemia.3 The world-wide incidence of ALL is about 3 per 100,000 individual.2 The incidence is highest at the age of 2-5 years.5 In Pakistan, multiple studies have been conducted on various aspects of ALL.6-8 According to a study carried out by Yasmeen N et al in 2009, ALL is the most common malignancy in children in Pakistan.6 The median age of ALL patients in Pakistan is 6 years,6,8 and male to female ratio is 1.7:1.8
The cure rate of ALL has reached almost above 80% due to improved treatment options.\textsuperscript{5,9,10} Despite of improved treatment options, the cure rates for ALL are lower in developing countries.\textsuperscript{11,12} While most ALL patients are cured with chemotherapy, 10–15% of the patients die of disease or treatment related complications.\textsuperscript{11,13} The mortality rate during induction therapy in the West is 1–2%.\textsuperscript{13-17} Infection is the commonest cause of death in the West, followed by hemorrhage and chemotherapy induced toxicity.\textsuperscript{15-17} Infection results from neutropenia and remains a significant cause of morbidity and mortality in children with ALL.\textsuperscript{1,13,15-19} Hemorrhage results from thrombocytopenia.\textsuperscript{1,15}

Eighty percent of the world’s children live in poor countries, where mortality rate is very high.\textsuperscript{20} High mortality rate in poor countries is due inadequate supportive care to the patients, that causes high treatment related mortality.\textsuperscript{5,12} This treatment related mortality is one of the major barrier to successful treatment of childhood acute lymphoblastic leukemia in the developing world.\textsuperscript{21}

Mortality data of the Western countries may not be representative for our population. This study was conducted at Children Hospital, PIMS (a tertiary care hospital), to find the induction death rate and analyze the causes of death in children during ALL therapy in our setup.

**Patients and Methods**

This cross-sectional study was conducted at Children Hospital, PIMS, Islamabad from 1st January 2014 to 30th September 2015. About 48 newly diagnosed cases of ALL in the age range of 1 -13 years, and both sexes were included in the study. Sample size was calculated by WHO calculator using confidence level of 95%, absolute precision of 5%, anticipated response of induction therapy of 98%,\textsuperscript{1,22,23} Using these statistical assumptions, minimum sample size obtained was 31.\textsuperscript{24} They were treated for ALL at Paediatrics Oncology department of Children Hospital, PIMS, according to the ALL-BFM Protocol. All children were followed during the induction therapy and mortality data including causes of death during this period was collected. The data was entered and analyzed on SPSS version 16.

**Results**

During the study period, a total of 48 newly diagnosed cases of ALL were included in the study. Children in the age range of 1 year to 13 years (mean age of 6.6 years ± 2.67 SD) were included in the study. Of these, 10 (20.8%) died during induction therapy. The mean age of patients who died during induction phase was 7 years ± 1.1 SD (range 3-12 years). Among these, six (60%) patients were 1-9 years of age and four (40%) were 10 or more than 10 years of age. Out of 10 patients, 5 (50%) patients were males and 5 (50%) were females and immunologically, majority was B cell type ALL (Table 1).

| Table 1: Characteristics of patients who died during induction (n=10) |
|-----------------------------|-----------------------------|
| **Age**                   | **Number** | **Percentage** |
| 1-9 years                  | 6           | 60            |
| >9 years                   | 4           | 40            |
| **Gender**                |             |               |
| Males                      | 5           | 50            |
| Females                    | 5           | 50            |
| **TLC at presentation**   |             |               |
| <50x10\(^9\)/L             | 8           | 80            |
| >50x10\(^9\)/L             | 2           | 20            |
| **Immunophenotype**       |             |               |
| Precursor-B cell ALL       | 9           | 90            |
| Precursor-T cell ALL       | 1           | 10            |

Out of 10 deaths, 5 (50%) patients died due to bleeding, 4 (40%) died of infection and 1 (10%) died of tumor lysis syndrome (figure 1). Bleeding manifested in the form of intracranial bleed, causing cerebrovascular accidents.

![Figure 1: Causes of death during induction therapy in patients of ALL](attachment:figure1.png)
Discussion

In West, survival of children with Acute Lymphoblastic Leukaemia is improved due to effective chemotherapy. The improvement in supportive treatment has caused great reduction in death rate during induction therapy. About 80% of the world's children live in countries where the resources are limited, and therefore, mortality rate is high. In the present study, out of 48 patients treated for ALL, 10 patients died during the induction phase while remaining 38 patients were able to complete induction therapy. So, the induction death rate in the present study was 20.8%. Out of 10 patients, 5 (50%) died due to bleeding in the form of intracranial bleeding, 4 (40%) died due to sepsis (infection), and 1 (10%) died due to tumor lysis syndrome. High mortality (20.8%) seen in our population was mainly due to haemorrhage and infections during the course of therapy. Similar experience has been reported by Mulatsih and Mostert from Indonesia who reported 29% and 23% mortality respectively. On the other hand, the incidence of treatment related death in the developed countries is about 2-3%. This clearly shows that there is a need to improve the supportive care for children receiving treatment for ALL in the developing countries.

According to one study done by Mushtaq N and Fadoo Z at Aga Khan University Hospital, Karachi, out of 121 patients, 9 (7.4%) patients died during the induction phase and infection was the most frequent cause of death. Their mortality rate during induction phase was much lower than that in the present study. In another local study done by Fadoo and Nisar in Karachi, reported that out of 582 children of ALL who were started with induction therapy, 50 (8.6%) died during this phase. Asim and colleagues reported the induction death rate of 12.8% of children with ALL. This value is somewhat closer to that reported in the present study. Maaz and colleagues reported induction phase mortality rate of 25% which is higher than reported in the present study. The present study reports induction death rate of 20.8%, which is much higher than that reported in developed countries where the reported induction death rate is less than 2%. The ALL-BFM 90 trial evaluated 2178 patients. Out of which, 22 (1.0%) patients died during induction therapy. The mortality rate of 1.0% reported in their study was much lower than that in the present study.

Mortality rate of 2.2% was reported by the study of Starry and colleagues. Connor and colleagues reported the death rate of 2.3% in their study, sepsis being the commonest (84% cases) cause of death. In the present study, bleeding was the major cause of death. This finding is inconsistent with other studies which report infection as the major cause of death. Choudhry and colleagues from India also reported infection as the major cause of death in children with ALL. Hargrave and colleagues also reported bacterial infections as the main cause of death during induction chemotherapy in ALL patients. High death rate in our study is due to low socioeconomic conditions of patients, failure to arrange platelet and blood, and non-compliance to treatment. High death rates can be improved by better supportive care of the patients in form of easy and prompt availability of platelet transfusions and meticulous antibiotic cover. Further studies are needed to identify and address the causes of increased induction mortality rate in our setup.

Conclusion

This study not only highlights the high rates of mortality during induction phase in our setup but also identifies that its main causes are bleeding and infections during the course of treatment. The death rate can be decreased with timely platelet and blood transfusions and infection control. This may be achieved by selecting appropriate antibiotics, ensuring availability of blood products and patient education.

References