Complications of Induction of Remission Chemotherapy in Childhood Acute Lymphoblastic Leukemia

Abstract

Background: Acute lymphoblastic leukemia is the most common malignancy in children. Myelosuppression amd immunosuppressions are anticipated complications of leukemia and chemotherapy, making patients liable to complications and require close monitoring of these patients. Awareness of complication patterns and prompt management may reduce treatment failure and death. This study aims to determine childhood acute lymphoblastic leukemia outcomes during induction of remission chemotherapy.

Methods: This cross sectional study was conducted at the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), from January 2013 to June 2013. Total 50 cases of acute lymphoblastic leukemia, aged 1 to 15 years, received induction of remission chemotherapy were included in this study. During induction chemotherapy, complications were recorded. At the end of induction, number of patients achieving remission and duration required to complete remission of induction schedule were also recorded.

Results: The mean age of presentation with ALL was 6.2±3.2 years with 56.0% male patients. During induction chemotherapy, 54.0% patients had febrile neutropenia, 48.0% had gastrointestinal complications, 46.0% had respiratory complications, 28.0% had haemorrhage and 12.0% had tumor lysis syndrome. Mortality rate was 12%. Three patients died from pneumonia, two from haemorrhage and one from pneumonia. 72% patients completed induction remission chemotherapy, 16.0% abandoned chemotherapy and 12.0% expired during chemotherapy.

Conclusion: Febrile neutropenia, gastrointestinal complications, respiratory complications and haemorrhage were common during induction of remission chemotherapy. 72% patients completed induction remission chemotherapy, 16.0% abandoned chemotherapy. Mortality rate was 12.0% and septicemia was the commonest cause of death.

Keywords: Acute lymphoblastic leukemia, Induction chemotherapy complications, febrile neutropenia.

Introduction

Acute lymphoblastic leukemia constitutes 97% of all childhood leukemias.[1] The incidence of acute lymphoblastic leukemia in the United States is 3-4 cases per 100,000 children. The peak incidence occurs between 2 to 5 years of age.[1]

Over the past several decades there has been remarkable improvement in the outcome of pediatric acute lymphoblastic leukemia.[2] Treatment of childhood acute lymphoblastic leukemia typically involves chemotherapy given for 2 to 3 years. The chemotherapy protocol includes induction of remission, consolidation, interim maintenance, delayed intensification and maintenance. Approximately 1-3 % of patients die during the induction of remission therapy from treatment related complications.[3]

Since myelosuppression and generalized immunosuppression are anticipated consequences of both leukemia and chemotherapy, patients must be closely monitored during treatment. A national multicenter study in UK on 1612 children, from 1985 to 1990 found that there were 2.3 % induction deaths; 84 % of

those deaths followed an infection.[4] In Central America, a study done from 2000 to 2008, researchers found that during treatment, 156 of 1670 patients died, of them 59 % died during induction of remission.[5] In Asian region, a study in Pakistan showed that out of 304 new cases registered between 2001 and 2005, 74 cases died during treatment, among them 52.7 % cases died during induction. Infection was responsible for death in 85% cases, 10.8% died from hemorrhage & 4% deaths were secondary to chemotherapy induced toxicity.[6] Another study done in Multan, Pakistan revealed that out of 38 patients enrolled between 2005 and 2008, 74% went into remission and 18% patients died due to febrile neutropenia & sepsis during the course of induction therapy.[7] Inmost contemporary clinical trials, <5 % patients die during induction of remission chemotherapy in developed countries.[8]

More than 80% of the world's children live in developing countries where the cure rate generally does not exceed 35 %.[6] Major causes of mortality in these countries include infection, hemorrhage and chemotherapy induced toxicity.[6] Other factors attributable to poor outcome include delay in diagnosis, suboptimal supportive care, co morbid conditions including malnutrition, abandonment of therapy due to low parental education and poor socioeconomic background.[6] Awareness about the pattern of complication & causes of mortality and prompt management of illness may reduce treatment failure and death.

Objectives

General objective: The objective of this study was to assess the outcome of childhoodAcute Lymphoblastic Leukemiaduring induction of remission chemotherapy.

Specific objectives:

1. To find out the complications during induction of remission therapy
2. To identify Mortality rate
3. To find out the causes of mortality
4. To find out the rate of achieving remission
5. To identify rate of premature abandonment of treatment

Methodology & Materials

This cross sectional study conducted at Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2013 to June 2013. A total 50 children with acute lymphoblastic leukemia, aged between 1 to 15 years, scheduled to receive induction chemotherapy at Department of Pediatric Hematology and Oncology of BSMMU are selected purposively and included in this study.

Inclusion:

1. Newly diagnosed acute lymphoblastic leukemia.
2. Ready to receive chemotherapy
3. Aged from 1 to 15 years

Exclusion criteria:

1. Patients aged less than 1year and more than 15 years
2. Patients whose parents did not give consent
3. Co-morbidities: Congenital heart disease, chronic kidney disease, connective tissue disorders, other chronic diseases, dimorphism etc.

Data collection: Data were collected using a pretested questionnaire regarding patient profile, initial clinical presentation, illnesses/complications during treatment, cause & number of death, number of patients achieving remission, number of patients with premature abandonment of treatment. Patients were visited and illness / problems were recorded daily. The induction of remission regimen was of UK ALL 2003 (Modified) protocol.

Ethical consideration: Ethical clearance was obtained from the concerned authority to conduct the research. Informed written consent was taken from the guardian before taking any interview. The consent form clearly described the purpose and method of the study, confidentiality of the interviews, risks and benefits of participating in the study, their rights to participate voluntarily and to refuse at any point in time without consequences.

Statistical analysis of data: Statistical analyses were carried out by using the Statistical Package for Social Sciences (SPSS) version 16.0. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages.

Results

Table 1: Demographic characteristics of the patients (50)

Characteristics		Number of patients	Percentage (%)
Age (years)	<5	19	38
	≥5	31	62
Mean±SD		6.2±3.2	
Sex	Male	28	56
	Female	22	44

Table 1 show the age and sexdistribution of the study patients; it was observed that 62.0% patients belonged to ≥5 year's age group. The mean age was found 6.2±3.2 years. Majority (56.0%) patients were male. The male: female ratio was 1.5:1.0.

Table 2: Distribution of the study patients by complication during induction of remission chemotheraphy (n=50)

Complication	Number of patients	Percentage (%)
Febrile Neutropenia	27	54
Gastrointestinal Complications		
Abdominal pain	10	20
Diarrhoea	9	18
Constipation	5	10
Respiratory complications		
Cough	11	22
Pharyngotonsillitis	6	12
Pneumonia	4	8
Otitis media	2	4
Haemorrhage	14	28
Tumor lysis syndrome	6	12
Skin infection	4	8

Hyperglycemia	2	4
Hypertension	1	2
Convulsion	1	2
Urinary tract infection	1	2

Table 2 shows complication of the study patients, it was observed that 54.0% patients had febrile neutropenia. Gastrointestinal Complications observed in 48.0%. Respiratory complications observed in 46.0% including pneumonia in 8.0% and otitis media in 4.0%. Twenty eight percent patients had haemorrhage, 12.0% had tumor lysis syndrome. Convulsionoccurred in 1 patient.

Table 3: Distribution of the study patients by cause of death (n=6)

Cause of death	Number of patients	Percentage (%)
Septicemia	3	50
Haemorrhage	2	33.3
Pneumonia	1	16.7

Table 3 shows cause of death of the study patients, it was observed that 3 patients died due to septicemia, 2 due to bleeding and 1 due to Pneumonia.

Table 4: Distribution of the study patients by average duration of completion of induction therapy (n=50)

Average duration of completion (weeks)	Number of patients	Percentage (%)
5	28	56
6-7	12	24
>7	10	20
Mean±SD	6.5±1.4	

Table 4 shows average duration of completion of induction therapy, it was observed that 56.0% patients completed induction of remission therapy in 5 weeks. The mean duration required to complete therapy was 6.5±1.4 weeks.

Table 5: Distribution of the study patients by outcome of induction remission chemotherapy (n=50)

Induction remission chemotherapy	Number of patients	Percentage (%)
Completed	36	72
Abandonment	8	16
Death	6	12

Table 5 shows outcome of induction of remission chemotherapy of the study patients, it was observed that, 72.0% patients had completed induction of remission chemotherapy and 16.0% patients abandoned therapy and 12.0% expired.

Discussion

This cross sectionalstudy was carried out with an aim to find out the complications, mortality rate, causes of death, rate of achieving remission and rate of premature abandonment of treatment during induction of remission chemotherapy in childhood acute lymphoblastic leukemia.

In the present study, it was observed that 62.0% patients belonged to ≥5 year's age group. The mean age was 6.2±3.2 years which ranged from 1 to 12 years. Fadoo et al.[9] found that median age at diagnosis was 6.6 years. The above findings are similar with the current study.It is documented that ALL occurs more in boys than girls at all ages[1]. Similarly, in this study it was observed that 56.0% patients were male and 44.0% female. The male: female ratio was 1.5:1.0. In Bangladesh, Yesmin et al.[10] found the maximum patients were male, where male to female ratio was 1.5:1, which is similar with the present study.

Complications during induction of remission therapy are associated with treatment failure & death. In the current study it was observed that during induction of remission, 54.0% patients had febrile neutropenia. In Singapore, Hamidah et al[11] found 73.2% cases of febrile neutropenia. Similarly, Greenberg D et al[12]reported that in febrile neutropenic patients, isolates included gram negative bacteria in 65%, gram-positive bacteria in 30% and fungi in 5% cases, among them 52.7 % cases died during induction.Due to logistic constraints, isolation of organism was not possible in all cases.

In this study it was observed that respiratory complications occurred in 46.0% of cases, out of which 8.0% was pneumonia and 4.0% was otitis media. Pneumonia is a major cause of death during induction chemotherapy for acute leukemia observed by Garcia et al.[13] The investigators conducted a retrospective cohort study of 801 patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) who underwent induction chemotherapy and found that pneumonia was present in 11.0%. The rate of pneumonia was higher in myelodysplastic syndrome and acute myeloid leukemia than in ALL ($p<0.05$). In another study Siegel et al.[14] evaluated the occurance of pneumonia in 844 children undergoing initial treatment for acute lymphoblastic leukemia and found that a total of 310 episodes occurred in 239 patients who were followed up for five to 36 months after diagnosis. Bacterial pneumonias occurred primarily during the first 20 days after diagnosis of ALL. No episode of Pneumocystis carinii pneumonia was noted before 40 days. In 80.0% of all episodes, a specific causative organism was not detected. In this study pneumonia was diagnosed on the basis of clinical findings and radiological evidence but organism isolation was not possible due to logistic constraints.

In the present study it was observed that convulsion occurred in 2.0% and Hypertension was present in 2%. Mandal et al[15] found that 9.0% children developed CNS complications during therapy. Posterior reversible leukoencephalopathy syndrome is a commonly reported complication (37-50%) presenting with seizures in up to 80.0% and hypertension in up to 86.0%. Intracranial haemorrhage is most serious complication. One patient died of intracranialhaemorrhage in this study. Bakk et al[16] in their study in US over 4917 newly diagnosed ALL patients aged from 0 to 28 years from 2009 to 2013, found that 13% patients developed hypertension.

Medical records of Children aged less than 14 years diagnosed with ALL were reviewed in a study of Saudi Arabia and found that 19% patients developed Tumor Lysis Syndrome. Hyperphosphatemia was found in 94.6% of the patients and hyperkalemia occurred in 23% patients. Hypokalemia was found in 12% of patients. Haemodialysis required in 5 patients. There were no deaths encountered due to TLS.[17] In the present study 12% patients developed TLS, all of them had initial WBC count more than 50 x 10^9/L and all of them had hyperuricemia, 66% had hyperkalemia and 50% had hypocalcemia. No patient died due to TLS. A study in Turkey over 214 ALL patients found that, hyperuricemia occurred in 12.6% of the patients with ALL. All hyperuricemic ALL patients had a leukocyte count more than 50 x 10^9/L at the time of diagnosis and none of the patients died; which is similar with the present study.[18]

Regarding the cause of death, it was observed in the present study that 3 patients died due to septicemia, 2 patients died from haemorrhage including 1 intracranial haemorrhage withconvulsion and 1 from pneumonia. Asim et al.[6] reported that infection was responsible for death in 85% cases, 10.8% died from hemorrhage & 4% deaths were secondary to chemotherapy induced toxicity. Another study in Multan, Pakistan revealed that out of 38 patients 18% died due to febrile neutropenia & sepsis during the course of induction therapy[7]. The St. Jude experience on death during induction therapy found that, out of 1011 patients enrolled in ALL treatment protocol, 1.4% died during remission induction therapy, 80% death occurred due to infection, but no death was due to metabolic complications or leukostasis.[8] In the present study, there was also no death from metabolic complication.

In the current study, it was observed that 56.0% patients completed induction of remission chemotherapy in due time that is in 5 weeks. The average duration needed to complete schedule was 6.5±1.4 weeks which ranged from 5 to 10.7 weeks. This delay occurred from interruptions of therapy due to various complications. Thus more severe complication leaded to more lengthening of chemotherapy schedule. This delay has an impact on patient's outcome and on the financial status of the family.

In this study, it was observed that, 72.0% patients completed induction of remission chemotherapy, 16.0% of cases abandoned induction remission chemotherapy and 12.0% patients expired. Fadoo et al.[9] showed that in their studyover a period of 3 years, 646 children with ALL successfully completed the induction phase and 69.6% achieved remission and cumulative treatment abandonment before and during the induction phase was 12.8%. Another study in Multan, Pakistan revealed that out of 38 patients 74.0% completed Induction remission chemotherapy.[7]

Limitations and recommendations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. Due to financial constraints microbiological confirmation of septicaemia and pneumonia could not be done.Further studies can be undertaken by including large number of patients for validation of this observation.

Conclusion

Febrile neutropenia, gastrointestinal complications, respiratory complications and haemorrhage were common complications during induction of remission chemotherapy. Seventy two percent patients achieved remission, mortality rate was 12.0% and septicemia was the commonest cause of death. Sixteen percent patients abandoned therapy.

Ethical approval

The Institutional Ethics Committee approved the study.

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