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ORIGINAL ARTICLE

Treatment-Related Mortality in Children with Acute Lymphoblastic Leukaemia at a Tertiary Care Hospital of Multan

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ABSTRACT

Background: The present study aimed to assess the frequency of treatment related mortality (TRM) among all ALL related mortalities recorded in the paediatric ward.

Methods: A cross-sectional study was undertaken at the Department of Pediatric, Children's Hospital and the Institute of Child Health, Multan, Pakistan between January 2021 and June 2022. The study enrolled all children under the age of 18 years who were diagnosed with acute lymphoblastic leukaemia. Data of individuals who died secondary to a relapsing or progressive disease or those who had not yet started chemotherapy were excluded. The main focus of the study was to measure TRM. All data were collected in pre-defined pro forma.

Results: A total of 205 deaths among ALL patients were reported during the study. Of these, 120 (58.54%) cases were associated with TRM. The most common type of ALL immunophenotype was B-cell ALL in 100 patients. Majority of the patients who suffered from TRM were at the induction phase i.e. 69 (57.50%). The most common cause of TRM was sepsis i.e. 100 (83.33%) cases. The second most common cause of TRM was haemorrhagic complications.

Conclusion: The results indicated that TRM was a significant contributor to treatment failure in this population. Out of a total of 205 deaths, more than half were attributed to TRM. Among the 100 patients evaluated, B-cell ALL was the most prevalent type. The majority of TRM cases occurred during the induction phase (57.50%), and sepsis was identified as the primary cause of TRM, followed by haemorrhagic complications.

Keywords: Acute lymphoblastic leukaemia, ALL, chemotherapy, febrile neutropenia, paediatric cancer, sepsis, treatment-related mortality, TRM

INTRODUCTION

Childhood blood and bone marrow are both affected by the illness known as acute lymphoblastic leukaemia (ALL). The mortality rate in children with ALL has significantly decreased in recent decades due to advances in treatment. However, treatment-related mortality remains an important consideration.[1-2]

Treatment-related mortality in children with ALL can occur as a result of toxic effects from chemotherapy, infections, and other complications. The risk of treatment-related mortality depends on several factors, including the child's age, overall health, and the aggressiveness of the cancer.[3-5]

To minimise the chances of treatment-related mortality, children with ALL receive multiple regimes of chemotherapy, radiation therapy, and in some instances, stem cell transplantation. These treatments help to kill cancer cells and mitigate the spread of the disease. It is important to note that advances in treatment and supportive care have greatly improved the survival rate of children with ALL. With early diagnosis and appropriate treatment, the majority of children with ALL can be cured.[6-7]

TRM is a substantial reason for treatment failure in low middle income regions such as Pakistan.[8] TRM refers to the death of a patient as a result of the treatment itself, rather than the underlying disease. There are several factors that can increase the risk of TRM in ALL patients, including [8-10]:

Advanced age: Older patients are more likely to experience complications from treatment, including TRM.

Poor performance status: Patients who are in poor physical condition before treatment may be more likely to experience TRM.

Co-existing medical conditions: Patients with coexisting medical morbidities, such as cardiac disease or pulmonary disease, may be at increased risk for TRM.

High-risk disease biology: Patients with certain genetic or biological markers that indicate a high-risk form of ALL may be more likely to experience TRM.

Intensity of treatment: More intense treatment regimens, such as stem cell transplantation, are associated with a higher risk of TRM. It is important to note that TRM can be influenced by multiple factors and can vary greatly between patients. Health care providers use a variety of tools and methods to assess a patient's risk of TRM and make treatment decisions that balance the potential benefits and risks.

In this present study, the authors evaluated the frequency of TRM and its causes among a cohort of ALL patients who died during the study period.

MATERIALS AND METHODS

A cross-sectional research was undertaken at the Department of Pediatric, Children's Hospital and the Institute of Child Health, Multan, Pakistan between January 2021 and June 2022.

A non-probability convenience sampling technique was utilised to recruit cases in the study. The study enrolled all children under the age of 18 years who were diagnosed with acute lymphoblastic leukemia (ALL). Data of individuals who died due to a relapsing or progressive disease or those who had not yet started chemotherapy were excluded. The study commenced only after receiving permission from the institutional ethics review board.

All individuals diagnosed with ALL were treated based on guidelines published by the United Kingdom Acute Lymphoblastic Leukaemia (UKALL).[11] The treatment for ALL involved five phases: i) remission induction, ii) consolidation, iii) interim maintenance, iv) delayed intensification, and v) maintenance. Patients admitted for febrile neutropenia caused by chemotherapy were given piperacillin-tazobactam and amikacin as empirical antibiotics, and antibiotics were adjusted based on clinical indications or culture and sensitivity reports. Data was recorded in a pre-established pro forma.

In the current study, specific definitions were created for certain terms. Patients with ALL were identified as per the results from blood tests or bone marrow biopsies that showed evidence of ALL through flow cytometry. Any death that happened during remission induction chemotherapy or during treatment following remission induction chemotherapy with a verified full remission was referred to as treatment-related mortality (TRM). Early disease-related death was defined as the passing of a clinically diagnosed individual before the start of treatment to induce remission. Sepsis was defined as indications of infection coupled with a systemic inflammatory response syndrome in order to further characterise the aetiology of TRM. The primary goal of the

research was to quantify TRM, and the underlying reasons were further divided into groups such sepsis, TLS, drug toxicity, hemorrhagic sequelae, thromboembolic events, and metabolic disturbances. Data was analyzed using SPSS 23, with categorical data being presented as frequencies and proportions and continuous data such as age presented as mean and standard deviation.

RESULTS

A total of 205 deaths among ALL patients were reported during the study. Of these, 120 (58.54%) cases were associated with treatment related mortality (TRM).

Table 1: Distribution of cause of death among ALL cases (n = 205)

Cause of death of ALL cases	N (%)
Treatment Related Mortality (TRM)	120 (58.54%)
Relapse related death	73 (35.61%)
Disease-related death	12 (5.85%)

A mean age of 7.00 ± 4.21 years was observed. In our study, 67(55.83%) were male and 53(44.17%) were females. The most common type of ALL immunophenotype was B-cell ALL in 100 patients. Majority of the patients who suffered from TRM were at the induction phase i.e. 69 (57.50%).

Table 2: Characteristics associated with Treatment related mortality (n = 120)

Parameter		N (%)
Mean Age (years)	7.00 ± 4.21	
Gender	Male	67(55.83%)
	Female	53(44.17%)
BMI	Underweight	86(71.6%)
	Normal Weight	20(16.6%)
	Overweight	6(5%)
	Obese	8(6.66%)
Immunophenotype	B-cell ALL	100(83.33%)
	T-cell ALL	20(16.67%)
Reason for Admission	Remission Induction	79 (65.83%)
	Febrile Neutropenia	36 (30.00%)
	Bleeding Symptoms	3 (2.50%)
	Drug Toxicity	2 (1.67%)
Phase of therapy	Induction	69 (57.50%)
	Consolidation	21 (17.50%)
	Interim Maintenance	15 (12.50%)
	Delayed Intensification	7 (5.83%)
	Maintenance	8 (6.67%)

The most common cause of TRM was sepsis i.e. 100 (83.33%) cases. The second most common cause of TRM was haemorrhagic complications.

Table 3: Causes of Treatment related mortality (n = 120)

Causes of TRM	N(%)
Sepsis	100(83.33%)
Haemorrhagic complications	13 (10.83%)
DrugToxicity	4 (3.33%)
Other	3 (2.50%)

DISCUSSION

We observed that treatment-related mortality (TRM) represented an important cause of treatment failure in this population. The study reported a total of 205 patient deaths, with 58.54% of those deaths being associated with TRM. B-cell ALL was the most common type of ALL immunophenotype among the 100 patients studied. Most of the patients who experienced TRM were in the induction phase (57.50%), and the primary cause of TRM was sepsis, which accounted for 83.33% of cases, followed by haemorrhagic complications.

The study titled "Treatment-related mortality in children with acute lymphoblastic leukemia in a low-middle income country" by Rahat-Ul-Ain, Mahwish Faizan, and Wasila Shamim conducted in Pakistan reported a treatment-related mortality (TRM) rate of 8.8%. This TRM rate was higher in patients who received chemotherapy alone compared to those who received both chemotherapy and radiotherapy. The most common cause of TRM was sepsis, followed by hemorrhagic complications. Another study conducted in Pakistan by Saeed et al. reported a TRM rate of 8.3% in paediatric ALL patients. This study also found sepsis as the most common cause of TRM. However, it's important to note that each study has its own unique patient population, treatment protocol, and follow-up period, which can affect the reported TRM rate.[12]

Cario et al. aimed to investigate the prognosis of children with ABL-class fusion positive B-cell acute lymphoblastic leukemia (B-ALL) treated according to AIEOP-BFM protocols, by analyzing relapse and treatment-related events.[13]

Treatment-related events was found to be correlated with poor prognosis in these patients. Specifically, the 5-year event-free survival (EFS) rate was 58% for all patients, and the 5-year overall survival (OS) rate was 68%. Among the 74 patients who experienced a treatment-related event, the most common events were haematological toxicity (68%) and sepsis (23%). The study also found that the cumulative incidence of relapse was 32%, and patients who relapsed had a significantly worse EFS and OS compared to those who did not. Additionally, patients who experienced treatment-related events had a significantly higher cumulative incidence of relapse compared to those who did not.[13] Overall, the study highlights the importance of monitoring and managing treatment-related events in addition to preventing relapse in the management of ABL-class fusion positive B-ALL, in order to improve prognosis and long-term outcomes for these patients.

The study by Loeffen et al. aimed to investigate the prevalence and risk factors of treatment-related mortality (TRM) in children with cancer. The study included 4,581 children who were treated for cancer in the Netherlands between 1990 and 2015. The study found that the overall prevalence of TRM was 2.5%, with the highest prevalence observed in patients with acute myeloid leukemia (AML) and central nervous system (CNS) tumors. In line with our study, Loeffen also revealed that the most common causes of TRM were infections (30%) and organ failure (25%). The study also found that the risk of TRM was higher in children who were younger at diagnosis, had more advanced disease, and received more intensive treatment.[14] Interestingly, the study also found that the prevalence of TRM decreased over time, from 4.4% in the period of 1990-1999 to 1.7% in the period of 2000-2015. This was attributed to improvements in supportive care, risk stratification, and treatment protocols.[14]

Another study by Kiem et al., aimed to identify the causes of death in childhood acute lymphoblastic leukemia (ALL) at Hue Central Hospital from 2008 to 2018. The study found that out of the 196 children diagnosed with ALL, 35 (17.9%) died, with infection being the leading cause of death, accounting for 57.1% of all deaths. The other causes of death included bleeding (14.3%), relapse (11.4%), and organ failure (8.6%). The study highlights the importance of infection prevention and control in the management of childhood ALL, as well as the need for early detection and appropriate management of complications to improve outcomes in children with ALL.[15]

Samra et al., reviewed the evolving therapy of adult acute lymphoblastic leukemia (ALL) and highlights the latest developments in treatment, including the use of immunotherapy and targeted therapies. The study suggests that the future of ALL treatment is likely to involve more personalized and targeted approaches based on genetic and molecular profiling, as well as the use of novel agents and combination therapies to improve patient outcomes.[16]

The present study's significant advantage was its population-based methodology that facilitated a more comprehensive analysis of treatment-related mortality (TRM) in the context of Pakistan. However, the study had a few shortcomings. For instance, it did not account for children who died before receiving chemotherapy or those who passed away while en route to the hospital.

Additionally, the TRM definition used in this research was consistent with some researchers but not all of them.[17,18]

To sum up, our study indicated that TRM is a significant problem in our setting that comprised more than one half of the deaths in our set up. Future research should aim to identify strategies that can enhance outcomes in similar contexts. Such interventions could comprise prioritizing platelet transfusion assistance, offering lodging options during the initial therapy phase, and providing aid regarding febrile neutropenia. Nevertheless, additional research is required to accurately specify the platelet product accessibility, the location of mortality during the initial phase, the time taken for empirical antibiotics in cases of febrile neutropenia, and the microbiology of infectious TRM, to establish well-informed interventional trials.

CONCLUSION

The present research examined 205 children diagnosed with ALL in the CH & ICH. The results indicated that TRM was a significant contributor to treatment failure in this population. Out of a total of 205 deaths, more than half were attributed to TRM. Among the 100 patients evaluated, B-cell ALL was the most prevalent type. The majority of TRM cases occurred during the induction phase (57.50%), and sepsis was identified as the primary cause of TRM, followed by haemorrhagic complications.

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