AUDIT ARTICLE

Treatment-related mortality in children with acute lymphoblastic leukaemia in a low-middle income country

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Abstract

Objective: To determine the proportion of treatment-related mortality among mortalities of paediatric acute lymphoblastic leukaemia and to identify probable causes and risk factors.

Methods: The observational retrospective study was conducted in February-March 2019 at the Department of Paediatric Haematology-Oncology and Bone Marrow Transplant, the Children's Hospital and the Institute of Child Health, Lahore, Pakistan, and comprised data of all paediatric patients of acute lymphoblastic leukaemia who expired during treatment from January 2017 till September 2018. Death due to relapse and deaths before treatment were excluded. Data was analysed using SPSS 16.

Results: Of the 247 deaths during the study period, 144(58.3%) were treatment-related mortality cases; 81(56.2%) males and 63(43.8%) females with an overall mean age of 5.0±3.83 years. The commonest cause was sepsis 126(87.5%), followed by haemorrhagic complications 11(7.6%), drug toxicity 4(2.8%), tumour lysis syndrome 2(1.4%) and thromboembolism 1(0.7%). Significant factors associated with treatment-related mortality were weight-for-age, immunophenotype, the reason for admission, and absolute neutrophil count ($p<0.05$).

Conclusion: Treatment-related mortality, though potentially avoidable, was found to be a major cause of death among paediatric patients of acute lymphoblastic leukaemia, and sepsis was the most common cause.

Keywords: Acute lymphoblastic leukaemia, Drug-related side effects, Adverse reactions, Developing countries, Infection.

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Introduction

During the past four decades, there have been exceptional gains in the overall survival (OS) in childhood cancer cases, especially in high-income countries (HICs) (>85%).[1,2] However, unfortunately, a substantial number of children with acute lymphoblastic leukaemia (ALL) are present in low- and middle-income countries (LMICs) where the survival rate in children with cancer is far inferior.[3,4]

Patients of paediatric ALL in Pakistan have been reported to present with higher risk features, have delayed presentation, inferior outcomes, and higher rate of infection, relapse and treatment abandonment compared to data from HICs.[5,6]

There are several reasons for this OS disparity, and drug/treatment toxicity leading to treatment-related mortality (TRM) is one of the most important causes.[7] Few studies that investigated TRM in LICs identified rates of ALL TRM from 11% to 21%.[8,9] Recent clinical trials have shown 5% patients dying during induction therapy[10-15] and in some trials, seemingly minor changes in therapy resulted in increased deaths due to toxicity.[16,17]

A vast majority of treatment-related complications are attributed to cytotoxic drugs and high-dose steroids that commonly cause immunosuppression and metabolic derangements. In the developing world, children often have suboptimal nutrition, poor personal hygiene and repeated admissions to hospital with frequent and extensive use of antibiotics increases the risk of infections. On the other hand, leukaemia itself may also cause complications, like haemorrhage, thrombosis, tumour lysis syndrome (TLS), and increased susceptibility to infections.[18] It is therefore imperative to identify the reason for mortality in this group of patients and pinpoint the areas for rectification to decrease TRM.

The current study was planned to determine the proportion of TRM among all mortalities encountered in paediatric ALL patients in an LMIC setting.

Materials and Methods

The observational retrospective study was conducted in February-March 2019 at the Department of Paediatric Haematology-Oncology and Bone Marrow Transplant, the Children's Hospital and the Institute of Child Health, Lahore, Pakistan, and comprised data of all paediatric ALL patients who expired during treatment from January 2017 till September 2018.

The Children's Hospital and The Institute of Child Health, Lahore is a tertiary care public-sector hospital which has the largest paediatric haematology/ oncology centre in the

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province of Punjab with a 60-bed inpatient unit catering around 100 patients daily. At this centre, curative as well as palliative treatment is offered free of cost not only to the patients who present from all over the country, but also from the neighbouring country Afghanistan.

Data included in the current study related to patients who had been admitted either for remission induction chemotherapy or any other treatment-related complication after achieving remission induction. Data of patients who expired due to either relapsed or progressive disease, or in whom treatment (chemotherapy) had not yet started was excluded. Data was retrieved using non-probability purposive sampling technique after approval from the institutional ethics review board.

All patients of ALL were treated according to United Kingdom Acute Lymphoblastic Leukaemia (UKALL) 2011 Interim Guidelines.[19] The treatment protocol broadly comprises 5 phases of treatment: remission induction, consolidation, interim maintenance, delayed intensification, and maintenance. Remission induction chemotherapy is of two types. Regimen A is a standard-risk option, while Regimen B carries high risk. Induction therapy comprises dexamethasone, vincristine, asparaginase, intrathecal methotrexate for central nervous system (CNS) prophylaxis. In Regimen B, daunorubicin is added. Standard or high-risk treatment regimen is decided as per the National Cancer Institute (NCI)-based risk stratification[20] and further phases of treatment are based upon response to treatment assessed by morphological remission in the bone marrow. Cytogenetics and Minimal Residual Disease (MRD) assessment facilities are not available at the study site. All further phases of chemotherapy after remission induction are categorised into Regimens A, B and C. Chemotherapeutic agents used in these phases are cyclophosphamide, cytarabine, asparaginase, vincristine, intrathecal, intravenous (IV) and oral methotrexate as well as doxorubicin and oral 6-mercaptopurine. The major differences among these therapy regimens lie between the consolidation phase of Regimen A with B/C, and the interim maintenance and delayed intensification phases of Regimen C with A/B with the addition of cytarabine blocks and escalating doses of methotrexate. Maintenance therapy for 2-3 years is composed of oral chemotherapy, comprising 6 mercaptopurine and methotrexate, with monthly vincristine and intrathecal methotrexate after every 3 months. In all newly-diagnosed patients, tumour lysis prophylaxis was given in the form of IV hydration (2-3L/m^2/day), oral allopurinol, and aluminum hydroxide. Trimethoprim-sulfamethoxazole prophylaxis was given to all patients who were on treatment for ALL. Empirical antibiotics piperacillin-tazobactam and amikacin were given to all patients who were admitted for chemotherapy-induced febrile neutropenia and later on antibiotics were tailored according to the clinical indications or culture and sensitivity reports.

For the purpose of the current study, operational definitions were formulated as given below:

Patients with ALL were diagnosed based on peripheral blood picture and/or bone marrow biopsy with immunophenotyping on flow cytometry suggestive of ALL.

TRM was defined as any death during remission induction chemotherapy or any death occurring on treatment after remission induction chemotherapy with documented complete remission.

Complete remission was defined as morphological remission with <5% blasts in bone marrow biopsy.

Early death due to disease was defined as any newly-diagnosed patient who expired before the institution of remission induction chemotherapy.

The underlying causes of TRM were also defined. Sepsis was defined as clinical or laboratory evidence of infection with systemic inflammatory response syndrome; lower respiratory tract infection (LRTI) was defined as the presence of suggestive auscultation findings (crepitation) along with radiological evidence of pneumonia on chest X-ray or computed tomography (CT) scan; CNS infection was defined as the presence of suggestive cerebrospinal fluid (CSF) findings and/or neuroimaging of meningitis/meningoencephalitis; gastrointestinal tract (GIT) infection was defined as the presence of acute gastroenteritis (loose stools > grade 3), typhlitis, or septic ileus as well as suggestive clinical signs and radiological studies; blood-stream infection was defined as blood culture positive for bacterial growth; urinary-tract infection (UTI) was defined as urine culture positive for bacterial growth (>10^5 CFU/mL); mucocutaneous infection was defined as clinical evidence of >grade 2 mucositis; invasive fungal infection was defined as radiological imaging suggestive of 2 or more systems involvement with fungal infection; TLS was defined as per Cairo-Bishop's classification[21] laboratory TLS and/or clinical TLS; pulmonary haemorrhage was defined as clinical evidence of pulmonary haemorrhage along with respiratory failure and suggestive radiological findings on chest X-ray; disseminated intravascular coagulation was defined as clinical evidence of bleed along with pancytopenia and deranged prothrombin time (PT) and activated partial thromboplastin time (aPTT) (D-dimers/fibrinogen degradation products are not available at the study site); intracranial haemorrhage/cerebral thrombosis was defined as CT or magnetic resonance

imaging (MRI) suggestive of cerebral haemorrhage/ thrombosis; drug toxicity was defined as per UKALL 2011 interim guidelines; and marrow failure was defined as two of three cytopenias: Absolute neutrophil count (ANC) <500/µl, platelet count <20,000/µl, reticulocyte count <40 x 10^9/L and bone marrow cellularity <25%.

The primary outcome measured in the study was TRM. The underlying TRM causes were further classified into sepsis, TLS, drug toxicities, haemorrhagic complications, thromboembolic phenomena, and metabolic derangements. Data was analysed using SPSS 16.

Results

There were 742 ALL patients registered during the study period and 247(33.2%) deaths. Of the mortalities, 144(58.3%) were TRM cases, 88(35.6%) deaths were because of relapsed disease and 15(6.1%) were early deaths due to the disease (Figure-1). Among the TRM cases, 81(56.2%) were males and 63(43.8%) were females, with an overall mean age of 5.0±3.83 years. The commonest cause was sepsis 126(87.5%), followed by haemorrhagic complications 11(7.6%), drug toxicity 4(2.8%), TLS 2(1.4%)

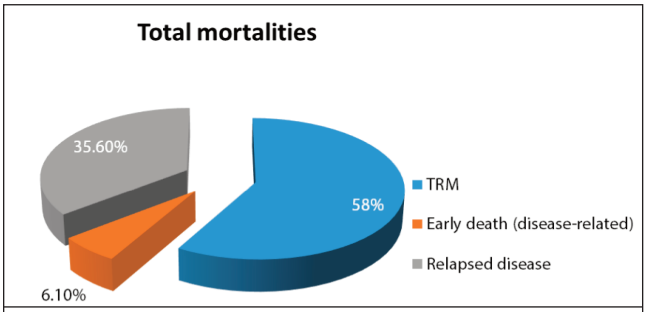

Figure-1: Percentages of period of haemorrhoids between the groups.

Table-1: Causes of treatment-related mortality (TRM) (n=144).

Cause of TRM	n (%)		n (%)
Sepsis	126 (97.5)	Lower respiratory tract infection (LRTI)	78 (54.2)
		Mucositis	63 (43.8)
		Bloodstream infection	41 (28.5)
		Gastrointestinal infection	20 (13.9)
		Invasive Fungal Infection	16 (11)
		Central nervous system (CNS) infection	15 (10.4)
		Urinary Tract Infection	2 (1.4)
		Mucormycosis	1 (0.7)
		Dental abscess	1 (0.7)
		Epstein-Barr virus (EBV) infection	1 (0.7)
Haemorrhagic Complications	11 (7.6)	Pulmonary Haemorrhage	5 (45.4)
		Intracranial bleed	4 (36.4)
		Disseminated Intravascular Coagulation	2 (18)
Drug Toxicity	4 (2.8)	Hepatic Failure during induction	2 (50)
		Methotrexate (MTX) toxicity	1 (25)
		Asparaginase-induced diabetic ketoacidosis (DKA)	1 (25)
Tumour Lysis Syndrome	2 (1.4)		
Thromboembolism (stroke)	1 (0.7)		

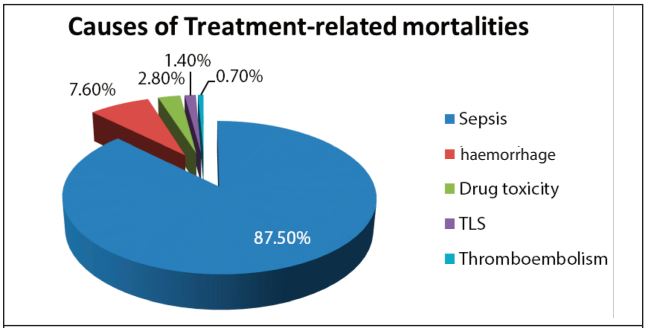

Figure-2: Causes of treatment-related mortalities (TRMs) among paediatric patients of acute lymphoblastic leukaemia (ALL).

Table-2: Factors associated with treatment-related mortality (TRM).

Factors		n (%)	*p*-value
Mean Age (years)	5.00+3.83		0.724
Gender	Male	81 (56.2)	0.187
	Female	63 (43.8)	
WFA	<5th percentile	41 (28.5)	0.007
	5th Percentile	4 (6.2)	
	10th Percentile	30 (20.8)	
	25th Percentile	32 (22.2)	
	50th Percentile	15 (10.40)	
	75th Percentile	3 (2.1)	
	90th Percentile	1 (0.7)	
	95th Percentile	2 (1.4)	
	98th Percentile	1 (0.7)	
Immunophenotype	B-cell ALL	129 (89.6)	0.032
	T-cell ALL	15 (10.4)	
Reason for admission	Remission Induction	98 (68.1)	0.000
	Febrile Neutropenia	42 (29.2)	
	Bleeding symptoms	3 (2.1)	
	Drug toxicity	1 (0.7)	
Mean Duration of admission (days)	16.97 +11.92		0.673
Phase of therapy	Induction	112 (77.8)	0.916
	Consolidation	14 (9.7)	
	Interim Maintenance	8 (5.6)	
	Delayed Intensification	5 (3.5)	
	Maintenance	5 (3.5)	
Treatment regimen	Regimen A	44 (30.6)	0.460
	Regimen B	83 (57.6)	
	Regimen C	17 (11.8)	
ANC on admission	>1500	80 (55.6)	0.962
	1000-1500	5 (3.5)	
	500-1000	9 (6.2)	
	300-500	17 (11.8)	
	<300	33 (22.9)	
ANC on death	>1500	8 (5.6)	0.000
	1000-1500	3 (2.1)	
	500-1000	4 (2.8)	
	300-500	10 (6.9)	
	<300	119 (82.6)	

SD: Standard deviation, WFA: Weight-for-age, ALL: Acute lymphoblastic leukaemia, ANC: Absolute neutrophil count.

and thromboembolism 1(0.7%) (Figure-2; Table-1).

Significant factors associated with TRM were weight-for-age (WFA), immunophenotype, the reason for admission, and ANC ($p<0.05$) (Table-2).

Discussion

In the current study, TRM constituted the major proportion (58.3%) of all deaths in patients with ALL. Therefore, a decline in the rate of TRM will have a significant effect on the outcome and OS of these patients.

Chemotherapy-induced febrile neutropenia predisposes the patients to a number of infections. Infectious complications/sepsis is the major cause of mortalities among all paediatric oncology patients[22-25] and the same was observed in the current study.

Wasting and undernutrition always pose challenges in paediatric patients and paediatric oncological patients pose even more challenges when concomitant chemotherapy-induced complications are present. It has already been proven that malnutrition has a significant effect on various aspects of management of paediatric ALL patients.[26-29] The remission induction phase of chemotherapy is the most toxic phase of treatment in ALL[26-29] and the current study also showed that most of the cases with TRM occurred during this phase of chemotherapy. The factors found to be statistically significant in association with the Treatment-related mortality in this study were: WFA of patients, the immunophenotype of ALL, the reason for admission in the hospital, and ANC at the time of death.

Conclusion

Treatment-related mortality, though potentially avoidable, was found to be a major cause of death among paediatric patients of acute lymphoblastic leukaemia, and sepsis was the most common cause. Infection prevention and control are vital in improving overall survival of ALL patients in developing countries.

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