HIGH INFECTION-RELATED MORTALITY IN PAKISTANI CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA DURING REMISSION INDUCTION CHEMOTHERAPY: REVIEW OF DATA FROM A SINGLE INSTITUTION

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Abstract

Purpose: Despite advances in the treatment of acute lymphoblastic leukaemia (A.L.L.), the outcome for children living in the developing countries is still poor. This is in large part due to high treatment-related mortality (TRM). This study was carried out to review the data and analyze the factors resulting in high TRM during remission induction chemotherapy.

Methods: Data for children treated at our centre during the calendar year 2007 were retrospectively analysed. Standard four-drug induction chemotherapy was used without risk stratification. Bone marrow evaluation was carried out at days 8 and 28. Cerebrospinal fluid analysis was carried out on day 1 and with each subsequent intrathecal chemotherapy injection. Modern supportive care facilities including antibiotics, nutritional support and intensive care unit were available.

Results: Eighty-one children were eligible for analysis. Median age was 5 years (range 2–16), 72% were male with M:F ratio of 2.5:1. Seventy-five (92%) children had precursor B-cell A.L.L. Only 2 children had central nervous system leukaemia at presentation. Median presenting white blood cell count was 8.83 (range: 1–446). Severe malnutrition (weight <5th centile for age) was seen in 42% of children. Median symptom duration was 6 (range 1–30) weeks at the time of presentation. Induction mortality was 25%. Induction mortality was 25.6% (n = 21). Twenty were related to infections, while more than half (52%) occurred as a result of an outbreak of Acinetobacter infection. Severe malnutrition and Acinetobacter infection (due to an outbreak in our unit during the study period) were highly predictive of TRM during remission induction chemotherapy.

Conclusions: Infection control measures, health education and reduction in treatment intensity may improve survival for children with A.L.L. in Pakistani population.

Key words: Acute lymphoblastic leukaemia in children, malnutrition, Pakistan, treatment-related mortality

Introduction

Acute lymphoblastic leukaemia (A.L.L.) is an eminently curable cancer of children, and an increasing number of groups are reporting long-term survival in excess of 80%. This success is attributable to advances in understanding of the disease biology and leukaemia cytogenetics, as well as advances in supportive care, in addition to the refinement of treatment such as minimal residual disease (MRD) analysis.[1-3] The same degree of success, however, has not been duplicated in resource-poor countries. This is thought to be related to a number of factors, including delayed presentation, lack of resources for individual families and low prioritisation of cancer in some health systems. Poverty predisposes children to malnourishment which may contribute to the severity of infections when exposed to anticancer chemotherapy. The poor outcome is also attributable to delay in diagnosis, interruptions in

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treatment due to its toxicity and poor compliance with treatment.[4,5] Lack of effective supportive care results in poor salvage rates when children experience treatment-related toxicity. Non-availability of sophisticated markers such as cytogenetic analysis and MRD analysis may also contribute at least to some extent to poor outcomes as these techniques can be useful in identifying children at high risk of relapse with standard treatment on the one hand and those requiring less intense therapy on the other.[6] In most recent series in the Western literature, reported induction mortality is <1%.[7] There are very few published studies reporting outcomes of A.L.L. from Pakistan.[8,9] Recently published series from India have reported induction mortality between 2% and 25%.[10-13]

Shaukat Khanum Memorial Cancer Hospital and Research Centre is a philanthropically supported, modern cancer centre in Lahore, Pakistan. After an initial clinical triage process, patients are registered and treatment is provided irrespective of their ability to pay for it. A number of patients travel long distances for treatment at this centre. Approximately 350–400 new children with different paediatric cancers are registered for treatment every year at this centre. Outcome analysis for A.L.L. is beyond the scope of this study. The objective of this study was to assess the toxicity of the regimen used in the study population and analyse factors resulting in early treatment-related death.

Methods

Data were analysed retrospectively for children treated at our centre for A.L.L. during the calendar year 2007. Patients who had received prior treatment and those who presented in relapse were excluded from analysis. SPSS statistical software version 16 was used for statistical analysis. Diagnosis was confirmed with bone marrow or peripheral blood immunophenotyping of leukaemic blasts by flow cytometery. Further bone marrow examinations were undertaken on day 8 for all and day 28 for patients who had either M2, M3 or hypocellular marrows on day 8. Cerebrospinal fluid (CSF) was obtained at the time of diagnosis and disease was categorised according to the accepted groups of central nervous system (CNS) 1, 2 and 3 status. Baseline cardiac left ventricular function was estimated by multigated acquisition scan before the first dose of daunorubicin. Baseline complete blood count and biochemical profile including liver function

tests, coagulation screening and serological screening for hepatitis B and C were performed at the time of diagnosis. All patients were admitted at the time of diagnosis. Induction chemotherapy was started after aggressive intravenous hydration for 24 h once the diagnosis of A.L.L. was established as above.

Chemotherapy

All patients received induction chemotherapy with intravenous vincristine (1.5 mg/m^2/dose on days 2, 9, 16, 23 and 30), intravenous daunorubicin (25 mg/m^2/dose on days 2, 9, 16 and 23); intramuscular l-asparaginase (*Escherichia coli* Asparaginase 6000 international Units/m^2/dose on days 2, 4, 6, 18, 10, 12, 14, 16, 18, 20, 22, 24 and 26) and dexamethasone(6 mg/m^2/day in two divided doses on days 1 through 28 followed by taper over 1 week). Intrathecal methotrexate was given (age-dependant dose) on days 1, 8 and 28 for CNS-negative patients and weekly for CNS-positive ones. Schedule is shown in Figure 1.

Supportive care

Institutional guidelines were followed for treating febrile neutropenia. These included broad-spectrum antibiotics, usually an antipseudomonal penicillin alongside an aminoglycoside as the first-line therapy and carbapenem as the second-line antibiotic therapy. Patient with central venous lines and those clinically suspected to have Gram-positive infections also received a glycopeptides (usually teicoplanin). Antifungal cover was added for fever unresponsive by 96 h. Antibiotic therapy was tailored for culture-proven infections according to the sensitivity of the organism. Supportive specialist advice for infectious diseases, gastroenterology and pulmonology was readily available by the on-site adult faculty. Neurology, nephrology and cardiology support was provided by visiting members of the faculty. Critically ill patients were nursed in our on-site intensive care unit where inotropic, ventilator and other interventional support was available. Product support was provided by the on-site blood bank and all blood products were screened for Hepatitis B and C and HIV.

Results

There were 81 evaluable patients enrolled for treatment during the study period. Median age was 5 years (range
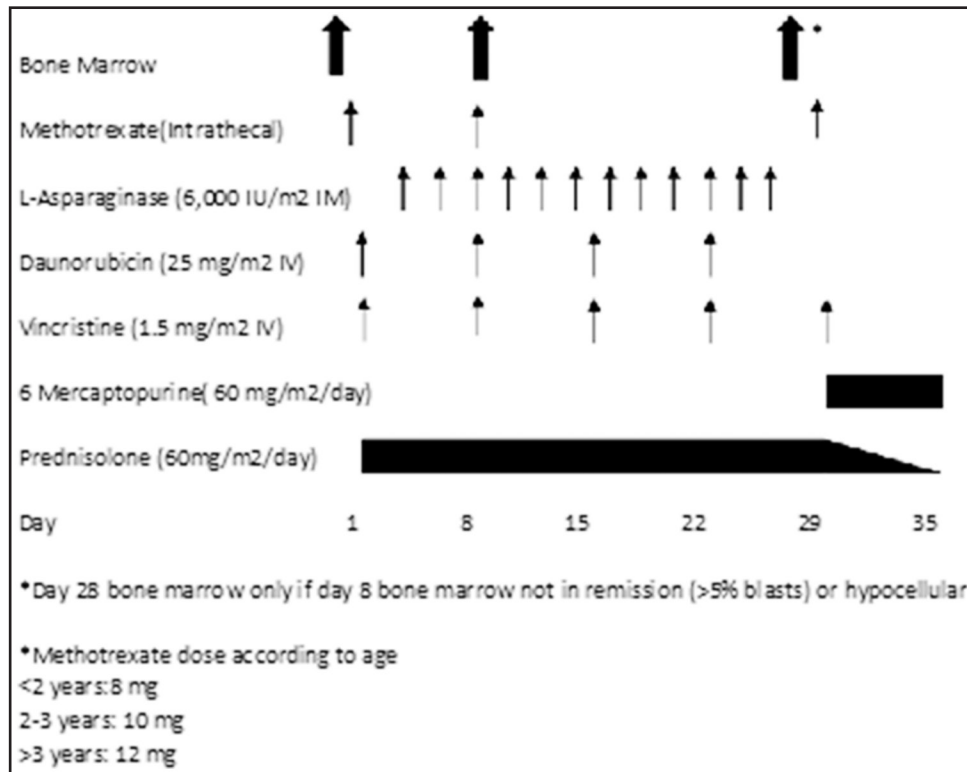
Figure 1: Treatment schema for remission induction chemotheraphy

2–16). Male-to-female ratio was 2.5:1. Seventy-five (92%) children had precursor B cell.

A.L.L., and the remaining 6 had precursor T-cell disease. Seventy-three (91%) children had CNS negative leukaemia, while only 2 had leukaemic blast cells in their initial CSF. Median presenting white blood cell count was 8.83 (range 1–446). Sixty-seven (82%) children fell in NCI standard-risk group. Severe malnutrition (weight<5th centile for age) was seen in 42% of children. However, the median plasma albumin concentration was 4.01 (range 2.53–4.75). Median symptom duration was 6 (range 1–30) weeks at the time of presentation.

Median time to initiation of treatment (days after registration at the hospital) was 14 (3–152) days. Patient characteristics are summarised in Table 1.

Response to treatment

More than half (54%) of children showed a rapid early response to treatment based on bone marrow morphology Table 2. Fourteen (17.3%) had M2 and 16 (19.8%) had M3

marrow on day 8. By day 28, however, all the surviving children had M1 marrow (<5% blasts).

Toxicity

Significant toxicities were seen in majority of children. These included Grade 3 or 4 haematological (88%), infection-related (75%), gastrointestinal (44%), pulmonary (21%), haemorrhage (13%), liver (12%) and neurological (7%) toxicities.

Grade 3 and 4 haematological toxicities included prolonged neutropenia, thrombocytopenia and anaemia. Infection-related toxicities included febrile neutropenia with clinical or culture-proven infections with (Grade 4) or without (Grade 3) evidence of septic shock. These included bacterial, fungal and viral infections. Gastrointestinal toxicities included severe mucositis, esophagitis, diarrhoea, colitis and ileus. Pulmonary toxicities included X-ray-proven pneumonia, oxygen requirement and mechanical ventilation. Haemorrhagic toxicities in our patients included severe post-surgical bleeding, gastrointestinal haemorrhage and CNS bleeding. Liver

Table 1: Patient characteristics (*n*=81)

Characteristics	n (%)	Additional information	Median	Range
Gender				
Male	58 (71.6)			
Female	23 (28.4)	Symptom duration (days)	42	7–210
Age (years)	2–16 (Median: 5)	Time to treatment (days)	14	3–152
NCI risk group		WBC (x109/L)	8.83	1–442
Standard risk	67 (82.7)	Albumin (mg/dL)	4.01	2.53–4.75
High risk	14 (17.3)			
Lineage				
Precursor B-cell	75 (92.6)			
Precursor T-cell	6 (7.4)			
Nutritional status				
Weight <5th centile	34 (42)			
Weight >5th centile	47 (58)			
CSF				
CNS1 (negative)	73 (90.1)			
CNS2 (trauma)	5 (6.2)			
CNS3 (positive)	2 (2.5)			

CSF: Cerebrospinal fluid, CNS: Central nervous system, WBC: White blood cell

Table 2: Bone marrow response at days 8 and 28

Day 8 bone marrow*	n (%)
M1	44 (54.3)
M2	14 (17.3)
M3	16 (19.8)
In evaluable	5 (6.2)
Day 28 bone marrow**	
M1	45 (100)

M status refers to percentage of blasts on morphological microscopic examination of bone marrow where M1 means blast count less than 5%, M2 5–25% and M3 more than 25% . *Two patients died before day 8 bone marrow examination was carried out. **Day 28 bone marrow examination was carried out for patients who were not in remission on day 8. ***In 15 patients, bone marrow examination was carried out on day 28 despite having M1 marrow on day 8 to confirm continuing remission. All patients had M1 marrow on day 28

Table 3: Grade 3 or 4 toxicities

Organ/system	n (%)
Haematological	72 (88.8)
Haemorrhagic	11 (13.5)
Infection	61 (75.3)
GI	36 (44.4)
Liver	10 (12.3)
Pulmonary	17 (20.9)
Neurological	6 (7.9)

toxicities included liver failure and CNS toxicities manifested in the form of convulsions. These data are summarised in Table 3.

Mortality

There were 21 deaths in the study population during remission induction chemotherapy or soon thereafter (before the start of consolidation). Median time to death was 20 days (range 9–41). Twenty of the 21 deaths were infection related (Gram-negative sepsis 15; Gram-positive sepsis 2; fungal infection 2 and pneumonia 1). The remaining one death was due to an intracranial bleed. These findings are summarised in Table 4 and 5.

Nineteen of the 20 infection-related deaths had culture-proven infections. A total of 41 microorganisms were isolated (23 were Gram-negative, 12 Gram-positive bacteria while the remaining 6 were fungi). Five patients had more than one positive culture while 14 patients had a single organism isolated from their body fluids.

Table 4: Cause of death (*n*=21)

Cause of death	n (%)
Gram-negative sepsis	15 (71.4)
Gram-positive sepsis	2 (9.5)
Fungal infection	2 (9.5)
Pneumonia	1 (4.8)
Intracranial bleed	1 (4.8)

Table 5: Death analysis (*n*=21; 25%)

Factors	n (%)	Significance
NCI risk group		
NCI standard risk	16 (23.8)	P=0.364
NCI high risk	5 (35.7)	
Morphology		
Precursor B	19 (25.3)	P=0.672
Precursor T	2 (33.3)	
Nutritional status		
Not malnourished	5 (17.8)	P=0.008
Malnourished	16 (30.1)	
Infection		
Acinetobacter	11 (91)	P=0.000
No acinetobacter	10 (14)	

Time to death: 9-41 days (median 21 days)

The most common organism isolated during the study period was Acinetobacter species (in 12 patients). All of the isolated Acinetobacter were multidrug resistant. This organism was also associated with a very high mortality (91%). Median time from the isolation of first Acinetobacter in body fluid cultures to death was 1 day (range 0–23).

Details of these organisms are given in Table 6 and Figures 1 and 2.

Five (35.7%) of the children in the National Cancer Institute (NCI) high-risk group died compared to 16 (23.9%) in NCI standard-risk group. However, these differences were not statistically significant.

Nutritional status

Thirty-four (42%) of children were severely malnourished i.e., weight less than 5th centile for age according to the Tanner-Whitehouse growth charts. Median serum albumin

Table 6: Characteristics of Acinetobacter species amongst the dead (*n*=12)

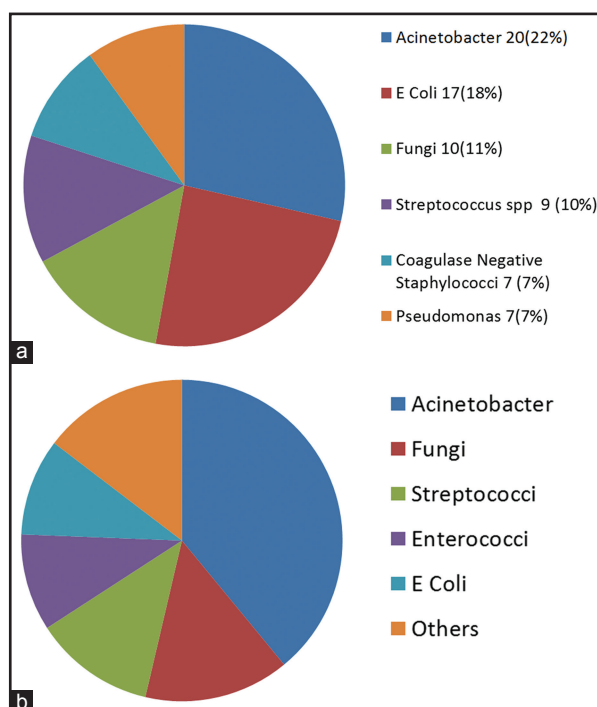| Characteristic	n (%)
Body fluid	
Blood	8 (75)
Tracheal aspirate	4 (25)
Sensitivity pattern	
Multidrug resistant	12 (100)
Sensitive	0
Blood counts	
Neutrophils <1.0	7 (58)
Neutrophils >1.0	5 (42)
Location	
ICU	7 (58)
Ward	4 (33)
Outpatient	1 (9)

ICU: Intensive care unit

Figure 2: (a) Microorganisms isolated during induction (*n*=90). (b) Microorganisms isolated from patients who later died (*n*=41)

concentration was 4.01 g/dL. 16 (47%) of severely malnourished children died compared to 5 (8.6%) who were not severely malnourished. Severe malnourishment was significantly correlated to the risk of induction

mortality ($P = 0.008$). However, a lower serum albumin was not correlated to mortality in our series.

Discussion

There are limited data on disease characteristics and outcomes of A.L.L. for Pakistani children.[8,9] To our knowledge, this is the first study from Pakistan reporting treatment-related mortality (TRM) for ALL induction therapy. Aziz *et al.* analysed the prognostic implication of presentation characteristics and outcome analysis using a modified BFM protocol in 2002. Reported induction mortality was in keeping with other published data from this part of the world. Their sample size was small, making it difficult to draw any definitive conclusions.[8] Khalid *et al.* have recently described a single-centre experience over 18 years using six different treatment protocols. Their starting sample size was 96. However, 52% were excluded for various reasons, leaving a small sample. Some of the traditional prognostic factors were confirmed while others were not found to be of any significance. They do not describe TRM.[9]

In the absence of consensus local guidelines and prospective cooperative trials, treatment of A.L.L. in Pakistan and indeed in many other developing countries of the world has historically been modelled on the templates of recognised international protocols. A standard four-drug chemotherapy regimen was used for all children during the remission induction phase without risk stratification. Template of the intermediate-risk arm of the UKALL 2003 study was followed, which was the current (at the time) CCLG UK protocol.

The results of our study show that there was a much higher than expected mortality (25.9%) in this population. This was primarily related to an outbreak of Acinetobacter infection during the study period. This organism, while of low virulence in the immunocompetent, is associated with a high mortality in the immunocompromised and seriously ill patients.[14] Our study population, which was at increased risk of mortality due to severe malnourishment and exposure to myelosuppressive chemotherapy, contracting Acinetobacter was highly predictive of mortality.

Successful implementation of infection control measures has since brought the incidence and resulting in

high mortality under control (hospital data, personal communication). If all the Acinetobacter cases are excluded from the analysis, induction mortality in the remaining group would be 11% that is more in keeping with other studies from the region.

Poor nutritional reserves, poor personal hygiene and overcrowded living conditions all contribute to poor chemotherapy tolerance, severe immune suppression and early death. Displacement from hometown has a dual impact on family incomes (i.e. losing primary income and incurring additional expense by staying away from home). Our results show significantly higher induction mortality in severely malnourished group. Others have also reported high TRM in malnourished children and in children belonging to poor socioeconomic and educational backgrounds.[5,15-17]

For several years, the poor outcome of childhood A.L.L. in this part of the world has been assumed to be at least partly related to adverse cytogenetic changes, hence the tendency of treatment with intensive regimens without stratification. Siraj *et al.* reported a higher incidence of adverse cytogenetics and a lower incidence of favourable translocation in Indian children with A.L.L. compared to Europeans and Americans. Faiz and Qazi also reported a less than expected favourable translocation t (12; 21) in Pakistani population.[18,19] However, even the highest estimates place the adverse cytogenetics group around 7–8%, which would still mean that over 90% of children could possibly be stratified to receive a lower intensity treatment. The importance of risk stratification is thus highlighted based on conventional, molecular and cytogenetic criteria to avoid over or under treatment.

Glucocorticoids are an essential part of A.L.L. treatment. Through the past many decades, prednisolone has been used by all major cooperative groups. Much is known about its efficacy and toxicity. Over the recent years, studies have shown that dexamethasone to be superior due to a relatively increased CNS penetration and reduction in the risk of CNS and bone marrow relapse. Mitchell *et al.* demonstrated that risk of CNS and non-CNS relapse in the group randomised to dexamethasone was half that of the prednisolone group in a randomised fashion. However, it is also known that dexamethasone is associated with increased risk of infections and other organ-system

toxicities.[20] Increased mortality individually as well as in combination with daunorubicin has been reported.[21,22] Inclusion of dexamethasone in the four-drug regimen may have had a compound contributory effect to the high toxicity profile of this regimen in our population.

We conclude that strict infection control measures are required to reduce induction mortality for A.L.L. Health education regarding improving hygiene and reducing overcrowding is paramount to reduce the infections and related mortality. Toxicity of treatment and induction mortality can be brought down by low-intensity regimen to low- and standard-risk patients. These changes have already been introduced and will need to be examined in future studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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