

Original Article

Death analysis of childhood Acute Lymphoblastic Leukaemia; experience at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan

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Abstract

Objectives: To analyze the common causes of death in childhood Acute Lymphoblastic Leukaemia (ALL) patients during therapy at Paediatric Oncology Department of Shaukat Khanum Memorial Cancer Hospital.

Methods: Retrospective descriptive study conducted at Paediatric Oncology department at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore Pakistan. All registered cases of ALL from 12 months to 18 years of age who expired between May 2001 to December 2005 were included. Mortality data was collected and analyzed regarding age, sex, WBC count, immunophenotype, treatment protocol, remission, and timing of death with respect to treatment protocol and the cause of death.

Results: Out of 304 new cases of ALL registered in the study period, 74 (24%) died during treatment. During induction 39 of 74 (52.7%) died, 33 (44.5%) in first remission and 2 (2.8%) before initiation of therapy. Infection alone or in combination with other factors was responsible for deaths in 63 of 74 (85%) cases. Septicemia, pulmonary and gastrointestinal infections were documented in 37/63 (58.7%), 44/63 (69%) and 8/63 (12.6%) cases respectively. Eight (10.8%) died due to haemorrhage. Three (4%) deaths were secondary to chemotherapy induced toxicity.

Conclusion: Infection is the major cause of mortality in ALL patients in our study population. To improve survival it is imperative to improve supportive care especially prevention and management of infection.

Keywords: Acute Lymphoblastic Leukaemia, Mortality, Infection, Developing countries (JPMA 61:666; 2011).

Introduction

The development of effective therapy for children with acute lymphoblastic leukaemia (ALL) is one of the great successes of clinical oncology, with long-term survival achieved in over 80% of patients and a 4-year event-free survival of approximately 92% in the western world.^{1,2} Improvement in survival achieved during the last three decades is attributable to better understanding of the disease process,

identification of risk factors predicting a poor outcome and risk-stratified treatment of patients. Advances in supportive care and availability of salvage options such as allogeneic stem cell transplant have further improved the survival.

However, more than 80% of the world's children live in developing countries, where the cure rate generally does not exceed 35%.^{3,4} Major causes of treatment related mortality in these countries include infections, haemorrhage,

and chemotherapy induced toxicity. Other factors attributable to poor outcome include delay in diagnosis suboptimal supportive care, co morbid conditions including malnutrition and abandonment of therapy due to low parental education and poor socioeconomic background.^{4,5}

There is scarcity of studies on causes of mortality during therapy for paediatric ALL from developing countries. Mortality data, available from Western studies may not be representative for our population. Therefore, a retrospective study was conducted at Paediatric Oncology department at Shaikat Khanum Memorial Cancer Hospital and Research Centre, (SKMCH&RC), Lahore, Pakistan to analyze the causes of mortality in children during ALL therapy.

Patients and Methods

This retrospective descriptive study was conducted at Paediatric Oncology department at SKMCH&RC. We reviewed the medical records of all paediatric patients treated for ALL between the ages of 1 and 18 years, registered at SKMCH&RC between 1st May 2001 to 31st December 2005. Medical records of the patients who died during this period were further analyzed for the purpose of this study.

Diagnosis of ALL at presentation was made on bone marrow morphology and immunophenotyping by standard techniques. Initial work up included full blood count and coagulation profile, full biochemical profile including liver function tests, renal profile and cardiac function assessment by performing a MUGA (Multigated Acquisition) scan.

Children were treated according to the institutional protocol based on the standard arm recommendations of current United Kingdom (UK) studies for ALL.⁶ Current UK guidelines were followed for the treatment of all leukaemics. For the first sixteen months of the study all new patients of ALL were treated according to the standard arm of the then current U.K trial of the Medical Research Council i.e. MRC ALL-97 (modified in'99).⁷ In September 2003 the same was converted into guidelines for treatment of ALL and named UKALL- 2003 which we followed until the end of the study period.

The UKALL-2003 protocol risk stratified patients according to age, initial white cell count and blast cell cytogenetics into progressively intensive treatment arms: Schedules A (low risk), B (intermediate risk) and C (high risk). Due to lack of cytogenetic facilities, we did not treat any of our patients on the low risk arm, all new patients initiated treatment on schedule B (intermediate risk) and some of them later moved to schedule C (high risk) if they showed Slow Early Response (SER) to treatment which was assessed by bone marrow examinations at day 8 and day 28 of induction.

Both MRC-ALL-97 (99) and UKALL 2003 consist of

the following 7 phases of treatment (Table-1).⁷

All patients were hospitalized for the initiation of induction chemotherapy. Tumor lysis prophylaxis with hyperhydration, allopurinol and aluminium hydroxide was started at least 24 hours before start of chemotherapy and continued for at least 4 days after. Intake, output and electrolytes were monitored carefully. Febrile neutropenias were treated with intravenous antibiotics. Fever was defined as a single oral temperature of $>38^{\circ}\text{C}$ or two readings > 37.5 at least 2 hours apart. Neutropenia was defined as absolute neutrophil count (ANC) of < 1000 . Our antibiotic policy was based on our hospital antibiograms. Patients with ANC 1000 - 500 and no co-morbidities were deemed low risk and treated with oral ciprofloxacin and augmentin with daily review, patients with ANC < 500 were treated with a combination of piperacillin- tazobactam and amikacin, Vancomycin or teicoplanin were added if central venous line infection was suspected. Anti-fungal amphotericin was added empirically if no culture positive and fever with neutropenia persisted for 96 hours or more. Pneumocystis carinii prophylaxis with cotrimoxazole was administered throughout treatment.

Data was analyzed according to age, sex, initial white blood cell (WBC) count, immunophenotype, treatment protocol, disease status, timing of death with respect to treatment protocol and the cause of death. Timing of death with respect to protocol was further categorized as death before initiation of therapy, death during induction and death in 1st remission which includes deaths in treatment phases other than induction.

The causes of death were divided into three major categories:

(i) Infections: These were further classified into (a) Microbiologically documented infections (MDI): Defined as episodes of infection with microbiological confirmation;. And (b) clinically documented infections (CDI): Defined as episodes with definite clinical signs and symptoms of infection, with or without radiologic evidence but lacking specific microbiological confirmation.

(ii) Haemorrhagic complications;

(iii) Chemotherapy induced toxicity.

The study was approved by the hospital ethics committee.

Data were analyzed using statistical package for social sciences (SPSS) version 10 and study was approved by the Hospital Scientific Review Committee.

Results

During the study period, a total of 304 new cases of ALL were registered. Of these 74 (24.3%) died during therapy. The median age at death was 5 years (range 1-18

Table-1: Treatment plan.

1. INDUCTION (4 weeks): Consisting of Vincristine, .Daunorubicin, Asparaginase Dexamethasone and intrathecal methotrexate
2. CONSOLIDATION (5 weeks): Cyclophosphamide, Cytosine Arabinoside, l mercaptopurine, Intrathecal . methotrexate
3. INTERIM MAINTENANCE-1 (8 weeks): Vincristine, Dexamethasone, Oral Mercaptopurine, Oral Methotrexate, Intrathecal Methotrexate.
4. DELAYED INTENSIFICATION-1 (7 weeks): Vincristine, Daunorubicin, Asparaginase, Dexamethasone, Cyclophosphamide, Cytosine Arabinoside, Oral Mercaptopurine, Intrathecal Methotrexate .
5. INTERIM MAINTENANCE-2 (8 weeks): Same as Interim maintenance 1
6. DELAYED INTENSIFICATION-2 (7 weeks): Same as Delayed Intensification 1.
7. MAINTENANCE (Total of 114 weeks for girls and 166 weeks for boys): Vincristine, Dexamethasone, Oral Mercaptupurine , Oral Methotrexate, Intrathecal Methotrexate.

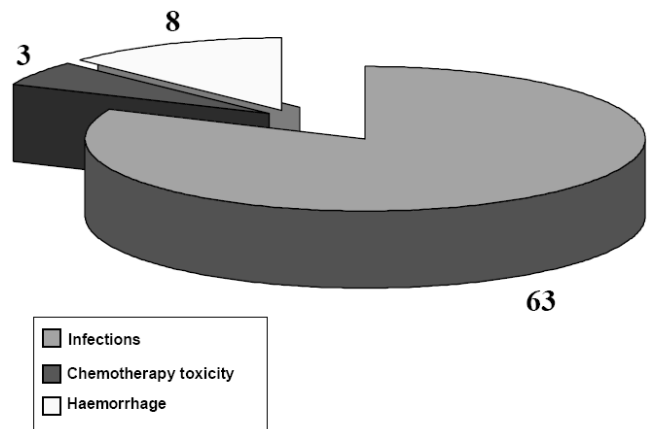
Table-2: Characteristics of 74 patients who expired.

Feature	No of patients	Percentage of patients
Age		
1-10 years	54	73
>10 years	20	27
Sex		
Male	41	55
Female	33	45
Initial WBC count		
<50,000	51	70
> 50,000	23	30
Immunophenotype		
Pre-B ALL	63	85
Pre-T ALL	11	15
Treatment protocol		
MRC ALL 99	25	36.5
UK ALL 2003	47	63.5
Disease status at death		
Remission	66	89
Not in remission	8	11
Timing of death with respect to protocol		
Before initiation of therapy	2	3
Induction	39	53
Consolidation	6	8
Interim Maintenance-1	2	3
Delayed Intensification-1	7	9.5
Interim Maintenance-2	1	1
Delayed Intensification-2	10	13
Maintenance	7	9.5
ANC at Death		
< 500 x 10 ⁹ /L	62	83.7
>500 x 10 ⁹ /L	12	16.3

years), Fifty four (73%) were between 1-10 years and 20 (27%) were more than 10 years of age. Forty one (55%) were males and 33 (45%) females. The initial WBC count at presentation was less than 50 x 10³/L in 51 (70%) and more than 50 x 10³/L in 23 (30%). Immunophenotyping performed by flowcytometry confirmed that 63 (85%) had precursor B

Table-3: Isolates of the septicaemia (n=37).

Isolates	Number
Gram Negative Bacteria	18
P. aeruginosa	05
E.Coli	05
Acinetobacter	03
K. Pneumoniae	03
Xanthomonas Maltophilia	02
Gram Positive Bacteria	10
MSSA	05
MRSA	03
Group D Streptococcus	01
S. epidermitis	01
Fungi	9
Candida Albicans	04
Aspergilosis	03
Candida non- albicans	01
Candida Tropicalis	01

**Figure: Causes of Death in ALL During Therapy.**

and 11 (15%) had precursor-T ALL.

Forty seven (63.5%) patients were treated according to the recommendations of UKALL 2003 trial and, 25 (36.5%) according to MRC ALL-97 (99). Two patients died before initiation of therapy.

At the time of death 66 (89%) patients were in remission while 8 (11%) were not in remission. There were 39 (52.7%) deaths during the induction phase while 33 (44.5%) deaths occurred in first remission. Two (3%) died before initiation of treatment (Table 2).

Causes of Death:

Of 74 deaths, 63 (85%) patients died of infection, 8 (10.8%) of haemorrhage and 3 (4%) died of chemotherapy induced toxicity (Figure). Thirty seven (58.7%) infective deaths were due to microbiologically documented infections (MDI) and 26 (41.3%) had clinically documented infections (CDI). Forty four (69%) had pulmonary infections and 8(12.6%) had gastrointestinal manifestations. Of the 37

deaths due to MDI, blood cultures grew gram negative bacteria in 18 (48.6%) cases, gram positive bacteria in 10 (27%) cases and fungi in 9 (24.3%) cases (Table-3).

Haemorrhage resulted in 8 (10.8%) deaths. Major sites of haemorrhage were intracranial in 5/8 (62.5%), gastrointestinal 1/8 (12.5%) and pulmonary in 2/8 (25%) cases each. Of the 3 (4%) chemotherapy related deaths, two as a result of acthracycline induced cardiotoxicity and one died of acute encephalopathy secondary to methotrexate.

Discussion

Over the last three decades, survival for children with acute lymphoblastic leukaemia has markedly improved due to intensive chemotherapy regimes. Improvement in antimicrobial therapy, supportive care and advances in intensive care has also enhanced overall survival by reducing the infection and toxicity related mortality and by shortening interruptions of chemotherapy.

Eighty percent of the world's children live in resource poor countries, where the mortality rate is still very high.^{3,4} In our series, the treatment was carried out following the recommendations based on the standard arms of current UK studies at the time. High mortality (24.3%) seen in our population was mainly due to infective and haemorrhagic complications of therapy rather than treatment failure or relapse. Similar experience has been reported by Mulatsih et al⁹ and Mostert et al⁴ from Indonesia who reported 29% and 23% mortality respectively due to complications in children while on treatment for ALL. Advani et al¹⁰ from India documented 16% toxic mortality in ALL patients. Contrary to this, the incidence of treatment related death in the developed countries is about 2.6-3.0%.¹¹⁻¹³ This disparity clearly highlights the need to improve the supportive care for children receiving treatment for leukaemias in the developing countries. It also demonstrates that heterogeneity in patient populations and resources can result in significant differences in outcome, even when the same treatment is used. Despite significant advances in supportive care, infections remain a major cause of therapy associated morbidity and death.⁸ Leukaemic patients receiving chemotherapy are vulnerable to severe and at times lethal infections due to breaks in epithelial barriers, interference with immune function, malnutrition and repeated therapeutic interventions. Involvement of the haematopoietic and lymphoid system itself by the malignant process also contributes to the immunocompromised state. Neutrophils provide the major cellular defense against most bacteria and chemotherapy induced neutropenia is well known to be associated with life-threatening infections, particularly if not treated immediately.¹⁴ In the present study, infections were responsible for 85 % deaths and 62/74 (83%) were neutropenic with ANC <500. Other groups have reported similar results. Choudhry et al¹⁵ from India found that infections either alone

or in combination with other factors were responsible for death in 42/55 (76.5%) of children with ALL. Similarly, Gao et al¹⁶ from China reported sepsis as major cause of mortality in ALL. Christensen et al⁹ from Nordic Society of Paediatric Hematology and Oncology (NOPHO) reported that 3% of children died while on treatment for ALL and infection was the major cause of death, accounting for 67% cases. Hargrave et al¹⁷ also reported bacterial infections as the main cause of death followed by fungal infection during induction chemotherapy in ALL patients.

In our series, 48.6% of all positive isolates were gram negative organisms while another 27% were gram positive organisms. In a recent report from Singapore Hamidah et al¹⁸ also found gram negative isolates in 73.2% cases of febrile neutropenia. Similarly, Greenberg et al¹⁹ reported gram negative bacteria in 65%, gram-positive bacteria in 30% and fungi in 5% cases of febrile neutropenia. These findings are consistent with our results.

Systemic fungal infections are a major cause of morbidity and mortality among patients with haematologic malignancies and neutropenia. Up to 20% of patients with neutropenia may experience an invasive fungal infection,²⁰ and autopsy studies suggest that invasive fungal infections are encountered in as many as 40% of patients with haematologic malignancies.¹⁷ In the current study, fungi were isolated in 9 cases (24.3% of all positive blood cultures). Rosen et al²¹ reported a linear increase in the incidence of fungal infections from 2.9% to 7.8% between 1996 and 2001 in paediatric haematology and oncology patients.

The major non-infective cause of treatment related death in leukaemic patients is haemorrhage. In our study, haemorrhage resulted in 10.8% of deaths and the main site of bleed was intracranial followed by gastrointestinal tract and lungs. Choudhry et al¹⁵ also found haemorrhage as the second major cause of mortality accounting for 12.7% of deaths. Hargrave et al¹⁷ reported bleeding as a constant and leading cause of non-infective death during the two decades of the Medical Research Council childhood lymphoblastic leukaemia trials from 1980 to 1997.

Chemotherapy related deaths vary among the different phases of chemotherapy. Most deaths occur during more intensive induction and intensification phases. In the current study, 53% deaths occurred during induction and 44% in first complete remission (CR1). Christensen et al¹² reported 33.9% deaths during induction and 66.1% deaths in CR1. Rubnitz et al¹³ similarly documented 58.3 % deaths during induction and 41.7% during CR1.

In our study Dexamethasone was used which may have contributed in increase mortality. However in MRC ALL/99 children were randomized to receive prednisolone versus dexamethasone throughout most of the treatment for

ALL. Event free survival at 3 years was 79% for the prednisolone arm and 85% for those receiving dexamethasone. There was increased morbidity in the dexamethasone arm. However there was no difference in life threatening toxicity or mortality. In CCG 1922, children with standard risk ALL were randomized to receive dexamethasone versus prednisone during induction and maintenance. That trial demonstrated a superior 4 year event free survival (88% vs. 81%) for children who received dexamethasone.²²

In our series 85% deaths occurred due to infection while on conventional chemotherapy. Although deaths due to infection may be impossible to completely eliminate, we believe that prompt and aggressive treatment of patients with the earliest signs of infection, even in the absence of fever, may decrease mortality. As our therapies continue to intensify, so should our vigilance and treatment of potential complications.

Conclusion

Infection remains the major cause of mortality in acute lymphoblastic leukaemia, both in the developed and developing world. Intensified chemotherapy regimens for high risk leukaemia have helped improve therapy outcome in the developed world. In resource poor countries, however, importing these regimens alone is not likely to improve overall outcome, unless simultaneous major reforms are made in the current supportive care facilities.

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