

Infections during Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia – Profile and Outcomes: Experience from a Cancer Center in South India

Abstract

Objective: The objective of this study is to describe the incidence, clinical, laboratory and microbiological profile, treatment, and outcome of infections during induction chemotherapy in children with acute lymphoblastic leukemia (ALL). **Materials and Methods:** This was prospective, observational study. All children aged 1–14 years, newly diagnosed to have ALL and attending the Pediatric oncology division at our center were included. Induction chemotherapy was administered as per a modified Berlin-Frankfurt-Münster protocol. The study period was from January 2014 to June 2015. **Results:** Two hundred and twenty-seven patients with ALL were included in the study. One hundred and fifty episodes of infection occurred among 117 patients. Major sites of infection were lung ($n = 35$) and gastrointestinal tract ($n = 30$). Blood cultures were positive in 45 episodes (30.6%) with Gram negative organisms being the predominant isolates. The most common organisms isolated were *Pseudomonas aeruginosa* and *Klebsiella* spp. The response to antibiotics was good with only 18% of episodes requiring a third-line antibiotic. One hundred and thirty-six (90.6%) episodes resolved without sequelae. Overall induction mortality (12 out of 227-5.3%) was mainly accounted for by infections. **Conclusions:** Infections are the major cause of mortality and morbidity in patients with ALL on induction chemotherapy. The outcomes are good for the majority of patients if they receive adequate antibiotics early in the course of infection.

Keywords: Acute lymphoblastic leukemia, induction chemotherapy, infections

Introduction

Infections are a major cause of mortality and morbidity in pediatric acute lymphoblastic leukemia (ALL), especially during induction chemotherapy. The chances of infection are more in these children due to the immunosuppression caused by the disease as well as the chemotherapy administered. Several studies have highlighted the fact that infections are more during induction chemotherapy compared to consolidation/maintenance chemotherapy. The data from major cooperative group trials also highlight the fact that the most important cause of treatment-related mortality (TRM) is infections. Information on the clinical and microbiological profile of infections is very important to reduce the morbidity and mortality and also to formulate an optimal antibiotic policy. The information on infections is more important in the Indian scenario where an improvement in the supportive care can probably improve our disease outcomes as

well. However, this information regarding infectious complications in cancer care centers in India is limited. Our study is an attempt to describe the incidence of infectious complications, their profile, and outcomes in a well-defined cohort of pediatric patients receiving intensive induction chemotherapy at a tertiary care oncology center in South India.

Materials and Methods

A prospective, observational study was done to describe the clinical and microbiological profile, treatment, and outcome of infections during induction chemotherapy in children with ALL. All children (Age: 1–14 years) newly diagnosed to have ALL and seeking the services of the Pediatric Oncology Division at our center during the study (January 2014 to June 2015) were included. Institutional review board and ethical committee clearance were obtained.

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Patients were divided into two risk groups (standard risk-SR and high risk-HR) based on age, presenting total white cell counts, immunophenotype, conventional karyotyping, FISH/PCR for Philadelphia chromosome-positive ALL, and steroid response. Induction chemotherapy was administered as per a modified Berlin-Frankfurt-Münster (BFM) protocol, for all. Phase IA of induction treatment consisted of three or four drugs depending on the risk stratification. From January 2014 to December 2014, standard risk patients received a three drug regimen (4 doses of vincristine (VCR), eight doses of L-asparaginase and steroids) while the high-risk patients received a four drug regimen (4 doses of VCR and daunorubicin (DNR), 8 doses of L – asparaginase and steroids). From January 2015, a revision in the treatment schedule was made with SR patients receiving two doses of DNR. The patients were then followed up regularly from start of induction till the completion of induction chemotherapy. They were evaluated further when they presented with clinical focus of infection or with fever.

Clinical data analyzed included the presence of fever, site of infection, and presence of hemodynamic instability. Laboratory data included the total count and differential count, platelet count, and C reactive protein (CRP). Blood cultures were taken from all patients. Two peripheral blood samples were taken if there was no central line. If the patient had a central line, one sample each was drawn from the peripheral and central line. Depending on the focus of infection, other relevant cultures were also taken. Chest X-ray was done only if clinically indicated. The data so obtained was also recorded on the pro forma.

On diagnosis of an infection, either due to fever or due to focus of infection, patients were started on antibiotics as per the standard antibiotic policy of the department – a-third generation cephalosporin with an aminoglycoside as first line, piperacillin – tazobactam ± aminoglycoside as second line and a carbapenem or colistin as third line antibiotic. If a Gram positive infection was suspected or cultures were positive for Gram positive organism, vancomycin, or linezolid was added. Antifungals were added empirically if fevers were persistent for more than 72–96 h or as treatment if cultures were positive. The treatment details with respect to the antibiotics used, change of antibiotics, addition of antifungals, and duration of treatment were also recorded. The need for supportive care in the form of use of inotropes and mechanical ventilation were also analyzed. The outcome of infection was also recorded. If chemotherapy was withheld due to the infection, the duration of withholding chemotherapy was recorded.

Results

Two hundred and twenty-seven patients were included in the study. The mean age at presentation was 5.87 ± 4.01 years. There were 130 males and 97 females with a male-to-female ratio of 1.34:1. One hundred and forty-four patients were in high-risk category and

83 patients were in standard risk category. All patients except one in the high-risk group were treated with a four-drug induction chemotherapy comprising VCR, DNR, L – asparaginase, and steroids. One patient was planned for three-drug induction because he had ataxia telangiectasia. Fifty-five patients in the standard risk group received 3 drug induction with VCR, L – asparaginase, and steroids and 28 patients received a regimen with 4 doses of VCR and 2 doses of DNR along with L – asparaginase and steroids.

Two patients were excluded – first patient with ALL on induction who developed varicella but was treated at another center, and hence, further details were not available; second patient who presented with tumor lysis syndrome expired within few hours of starting steroids and was excluded from the study.

Episodes of infection

150 episodes of infection occurred among 117 patients. Of the 83 SR patients, 38 developed infection, i.e., 45.8% and of the 144 HR patients, 79 developed infection, i.e., 54.9%. Fever was present at presentation in 112 episodes (74.6%) and absent in 38 episodes (25.4%).

Major sites of infection were lung ($n = 35$) and gastrointestinal tract (GIT) ($n = 30$). No definite focus of infection was evident in 28% ($n = 42$). Table 1 shows the major sites of infection.

Evidence of hemodynamic instability were seen in the form of tachycardia ($n = 43$), hypotension (septic shock) ($n = 21$), and tachypnea ($n = 23$).

Laboratory investigations

CRP was done in 131 episodes. Values were <1 mg/dL in 26 episodes, 1–9 mg/dL in 76 episodes

Table 1: Sites of infection

Focus of infection	n (%)
Lung	35 (25)
Gastrointestinal tract	30 (20)
Skin and subcutaneous tissue	14 (9.3)
Mucositis	8 (5.3)
Urinary tract	4 (2.6)
Perianal	3 (2)
Lung + mucositis	3 (2)
Central nervous system	2 (1.3)
Central venous catheter	2 (1.3)
Lung + gastrointestinal tract	2 (1.3)
Otitis media	1 (0.6)
Skin + central venous catheter	1 (0.6)
Skin + otitis	1 (0.6)
Lung + skin	1 (0.6)
Varicella zoster	1 (0.6)
Fever without focus	42 (28)
Total	150

and more than 9 mg/dL in 29 episodes. Platelet counts were $<20,000/\text{mm}^3$ in 51 episodes, $20,000\text{--}50,000/\text{mm}^3$ in 45 episodes, and $>50,000/\text{mm}^3$ in 54 episodes.

Profile of microorganisms

Blood cultures were done in 147 of the 150 episodes. There were 45 positive blood cultures, i.e., 30.6% of patients had a microbiologically defined infection. Most of the isolates were gram negative organisms ($n = 36$; 80%). Three isolates were purely fungal – 6.7%. Two more fungal isolates occurred – in combination with pseudomonas. Table 2 shows the profile of microorganisms isolated from the blood.

Treatment details

One hundred and twenty-seven episodes were initially treated with first-line antibiotics, 19 episodes with second-line antibiotics and 4 episodes with third-line antibiotics based on the severity of infection. Eventually, 127 episodes received first line, 47 episodes received the second line, and 28 episodes received third-line antibiotics as per institutional protocol. Antifungals were given in 29 episodes (19.3%). 24 among them were empirical and the rest based on positive culture reports. Intensive supportive care in the form of inotropes or mechanical ventilation was required in 17 episodes (11.3%). Inotropes were required in 15 episodes of septic shock – dopamine/adrenaline/noradrenaline. Ventilation support was required in six episodes (4%) of whom one survived and 5 expired.

Outcome of infection

One hundred and thirty-six (90.6%) episodes resolved without sequelae. Twelve patients (8%) died (One of them had varicella with hepatitis and coagulopathy). Two patients survived with sequelae – one with perforation peritonitis requiring colostomy and one with persistent empyema requiring decortication. Overall, induction mortality (12 out of 227-5.3%) was mainly accounted for by infections.

Table 2: Profile of microorganisms isolated in blood culture

Organism	n
<i>Pseudomonas aeruginosa</i>	9
<i>Klebsiella</i> species	8
<i>Acinetobacter</i>	6
<i>Escherichia coli</i>	5
<i>Staphylococcus aureus</i>	2
Methicillin-resistant Coagulase negative Staphylococci	2
Methicillin-resistant <i>Staphylococcus aureus</i>	1
<i>Aeromonas</i>	1
<i>Burkholderia</i>	1
Nonfermenting Gram-negative bacilli	1
Nonhemolytic Streptococci	1
<i>Candida</i>	3
Mixed growth of 2 organisms	5
Total	45

Chemotherapy had to be withheld on 47 episodes. The median duration of withholding chemotherapy was 6.85 days.

Outcome of induction chemotherapy

Of the 227 patients, 208 patients (91.6%) attained remission at the end of 4 weeks of induction chemotherapy. 12 patients (5.3%) expired during induction. 6 patients (2.7%) did not attain remission at the end of 4 weeks of induction chemotherapy. One patient (0.4%) was given an extended induction for 6 weeks as an individualized decision based on multiple factors.

Analysis of risk factors for infection or outcome

We analyzed four factors using Chi-square test to assess whether they predict an increased risk of infection – age, gender, risk group, number of drugs received during induction chemotherapy. However, there was no statistically significant association.

CRP, blood culture positivity, and platelet count were assessed with respect to the outcome of infection using Fisher's exact test. None of the factors showed a statistically significant association with outcome of infection.

Analysis of factors affecting mortality

Mortality was assessed using Fisher's exact test with respect to the following factors: Age, risk, number of drugs used in induction chemotherapy, number of episodes of infection, tachypnea, tachycardia, hypotension, CRP, and platelet count. The only factors found to be significantly associated with mortality were tachycardia ($P < 0.001$), tachypnea ($P < 0.001$), and hypotension ($P < 0.001$). The presence of positive blood cultures also did not affect mortality when assessed using Chi-square test.

Discussion

Our study was done to assess the incidence of infections during induction chemotherapy in children with ALL and to assess the clinical profile, laboratory parameters, microbiological profile, and the outcome of infections. The induction phase was selected to study the infection profile because this is the phase during which chance of infection is highest both due to the immunosuppressive nature of disease and the chemotherapy regimen used. In a study by Bakhshi *et al.*, 166 of 222 (74.7%) episodes of infections in ALL occurred during induction and intensification/consolidation phase of chemotherapy and only 56 episodes (25.3%) occurred during maintenance phase of chemotherapy.^[1]

Our study was done over a period of 1½ years and included 227 patients. 51.5% of patients developed at least one episode of infection during induction. The risk group or the induction protocol (4 drugs versus 3 drugs) did not affect the rates of infection though we would have expected a higher rate of infection with the 4 drug regimen.

The most common focus of infection was lower respiratory tract (25%, $n = 35$) followed by GIT (20%, $n = 30$). Around one-third of patients had no definite focus of infection. In the previously quoted study by Bakhshi *et al.*, pulmonary infections were the most common site of infection (27.3%), followed by HEENT (22.9%), gastrointestinal tract, blood, urinary tract and connective tissue, with a higher incidence of infections during the intensive phases of chemotherapy.^[1] In a study from Egypt which included both ALL and AML patients during induction chemotherapy, oral mucositis was the most frequently detected site of infection (52%), followed by skin (34%), GIT, and lower respiratory tract infections.^[2]

The danger signs noted in these episodes were tachycardia (28.6%), hypotension (14%), and tachypnea (15%). The presence of these danger signs had a statistically significant association with mortality. Hence, the occurrence of any of these signs during an episode of infection should alert the clinician regarding the severity of infection.

CRP levels were more than 1 mg/dL in 80% of episodes with 22% episodes having a CRP level more than 9 mg/dL. However, the CRP levels did not correlate with the outcome of infection or mortality. Another laboratory parameter analyzed was the platelet count. Studies have shown that presence of thrombocytopenia in sepsis is associated with increased mortality and poorer outcomes.^[3,4] In our study, low platelet count did not show a statistically significant association with the outcome of infection ($P = 0.058$) or mortality ($P = 0.062$). However, the P values showed a trend toward significance. A statistical significance could not be reached probably due to the small sample size.

Around one-third of patients had a positive blood culture (30.6%) with 80% of the isolates being gram negative organisms. Nearly 7% of isolates were fungal. Microbiological data from various other oncology centers in India also show a predominance of Gram-negative organisms which was observed in our study as well.^[5-9] Further analyses did not show a significant correlation between blood culture positivity and laboratory parameters such as CRP or the outcome of infection.

Infections were the major cause of mortality during induction in our series. In an analysis of mortality in children with ALL from PGI Chandigarh by Marwaha *et al.*, the induction mortality during the period 1998–2006 was 10% ($n = 40$) of which 20 had died of infection.^[10] Large cooperative groups have also published data pertaining to their TRM and have shown that the major cause of TRM is infections and especially so during the induction period. In UK ALL 2003 trial, sepsis was the most common cause of TRM and risk of infection-related mortality was higher during induction.^[11] In an analysis of the St. Jude experience of deaths during induction therapy and first remission of acute leukemia in childhood, infection was

the most common cause of death. Fourteen died during disease remission induction: 11 died of infection, and 3 died of noninfectious causes.^[12] Similar results have also been published by the Austrian BFM group and NOPHO group.^[13,14]

Conclusions

Infections were a major cause of morbidity and mortality in pediatric ALL during induction chemotherapy, in our series. Around half of the patients had at least one episode of infection; Gram-negative organisms were the predominant isolates in blood culture. Most infections respond well to standard antibiotic regimens.

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Conflicts of interest

There are no conflicts of interest.

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