

Outcome of Childhood Acute Lymphoblastic Leukaemia after Induction Therapy – Three-Year Experience in a Tertiary Care Hospital in Bangladesh

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Abstract

Background: The incidence of different malignancies is increasing among the world populations. Acute lymphoblastic leukaemia (ALL) is the most common of all the paediatric malignancies. Response to induction therapy is one of the most important predictors of long term outcome of ALL. **Objective:** To see the immediate outcome of paediatric ALL patients following induction therapy. **Materials and Methods:** This retrospective study was conducted from January 2013 to December 2015. Total 221 paediatric ALL patients were included in this study. Diagnosis was based on history, examination, blast cells count on peripheral blood film and bone marrow study, CSF study and immunophenotyping of peripheral blood/bone marrow aspirate in patients who were financially capable. Among them, parents of 40 (18%) patients did not agree to start chemotherapy. According to Modified UK ALL 2003 protocol (Regimen A & B) 181 patients were given induction therapy (vincristine, prednisolone, L-asparaginase, and daunomycin) in high risk patients. Among them 14 patients discontinued, 10 patients died during chemotherapy and rest 157 patients completed induction phase. Bone marrow study was repeated after completion of induction therapy and remission pattern was seen. **Results:** Out of 157 chemotherapy completed patients, 137 (87%) went into complete remission (<5% blast cells in bone marrow), 14 (9%) into partial remission (5–25% blast cells in bone marrow) and 6 (4%) was not in remission (>25% blast cells in the bone marrow). Ten (5.5%) patients died due to bleeding, febrile neutropenia and sepsis during the course of induction therapy. **Conclusion:** ALL in children is curable with effective chemotherapy. Poverty, ignorance and misconception regarding outcome are responsible for refusal and discontinuation of chemotherapy in third world countries like Bangladesh. Mortality and treatment cost can be reduced with the improvement of the facilities for isolation, barrier nursing and supportive treatment, and by creating awareness.

Key words: Acute lymphoblastic leukaemia; Induction therapy; Outcome

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Introduction

Acute leukaemia is the most common form of malignancy in children, comprising approximately 30%

of all childhood malignancies.¹ Of acute leukaemias, acute lymphoblastic leukaemia occurs five times more commonly than does acute myeloid leukaemia.² A

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sharp peak of ALL incidence is observed at 2–5 years of age.² There has been a gradual increase in the incidence of ALL in the past 25 years.³ Hopefully survival rates for ALL have improved dramatically since 1980s with a current five-year overall survival rates greater than 85%.⁴⁻⁶ This improvement is due to treatment of a large number of children in sequential standardised research protocols. Treatment of children with ALL is divided into several stages: remission induction, consolidation or intensification, and maintenance (continuation) therapy with CNS prophylaxis therapy generally provided in each stage.

The goal of induction therapy is to bring the disease into remission (patient's blood counts return to normal and bone marrow shows no signs of disease). Usually three-drug induction therapy using vincristine, prednisolone/dexamethasone, plus L-asparaginase in conjunction with intrathecal therapy (IT) results in complete remission rates of greater than 95%.⁷⁻⁹ Patients with increased risk require anthracycline (e.g., daunomycin). Protocols using this 4-drug combination with intensive consolidation and maintenance therapy uniformly demonstrate improved overall remission duration, even for high risk patients.¹⁰⁻¹¹

The initial response to remission induction therapy is one of the most important prognostic factors in acute lymphoblastic leukaemia (ALL). Patients who respond slowly have a high risk of relapse, while those who fail to attain a complete remission within 4–6 weeks of treatment have dismal prognosis.¹² This study analyses the results of three to four-drug induction chemotherapy in the department of Paediatric Haemato-Oncology of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.

Materials and Methods

This retrospective study was conducted in the department of Paediatric Haemato-Oncology of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from January 2013 to December 2015.

Total 221 newly diagnosed paediatric patients of ALL during this period were included in this study. Patients who had relapsed ALL, infantile leukaemia, and who were given chemotherapy elsewhere were excluded from the study. Patients remained admitted in the oncology ward for the whole duration of induction therapy.

After history and clinical examination, CBC, peripheral blood film and bone marrow biopsy/aspirate were seen for detection of blasts cells. Immunophenotyping by flow-cytometry was done on peripheral blood sample or bone marrow aspirate for patients who were financially capable. Serum electrolytes, liver and renal function tests, tumour lysis profile, blood culture, CSF and chest radiography were also done. Patients were stabilised haemodynamically by packed cells transfusion if haemoglobin level was less than 8 gm/dL, platelets transfusion if platelet count was $<20,000/\text{mm}^3$. Tumour lysis prophylaxis was started in the form of adequate hydration, allopurinol, phosphate binder and treatment of hyperkalemia and hypocalcaemia where needed. For febrile neutropenia (ANC $<1.0 \times 10^9/\text{L}$ plus fever $\geq 38^\circ\text{C}$ (100.4°F) for >4 hours or single spike of $\geq 38.5^\circ\text{C}$ (101.3°F) proper antibiotics were started.

Parents of 40 patients out of 221 did not agree to start chemotherapy. In the rest 181 patients four-drug induction therapy was started according to Modified UKALL 2003 Protocol (Regimen A&B) with vincristine, dexamethasone/prednisolone, L-asparaginase, and daunomycin. Intrathecal methotrexate, cytarabine and hydrocortisone were given on day 1 and day 28. Among them 14 patients discontinued chemotherapy and 10 patients died during chemotherapy. The rest 157 patients completed induction phase. Bone marrow study was repeated at the end of induction therapy to see the remission. Remission pattern was noted – whether complete remission ($<5\%$ blasts cells in the bone marrow), partial remission (5–25% blast cells) or no remission ($>25\%$ blast cells).

Results

Among the 221 patients, 146 (66%) were males and 75 (34%) were females. Mean age of the subjects was 5.5 years (2–14 years).

Pallor was noted in 201 (91%), fever in 186 (84%), bleeding manifestation in 99 (45%), hepatosplenomegaly in 177 (80%), lymphadenopathy in 139 (63%) and mediastinal mass in 7 (3.1%) patients (Fig 1).

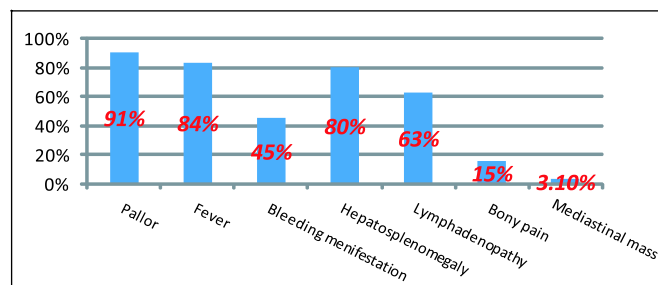


Fig 1. Clinical manifestations of study subjects (n=221)

Total leucocyte count (TLC) was $<50,000/\text{mm}^3$ in 152 (69%) and $>50,000/\text{mm}^3$ in 69 (31%) patients. Blast cells were detected in 201 (91%) patients in peripheral blood film (PBF) with range of 2–96% and not detected in 20 (9%) patients. All the 221(100%) patients showed blast cells in bone marrow biopsy/aspirate. CSF from all the patients showed no blast cell (Fig 2).

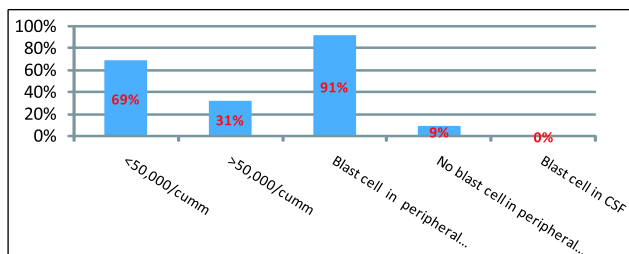


Fig 2. Laboratory profile of study subjects (n=221)

Parents of 40 (18%) patients refused to start chemotherapy and parents of 14 (6%) patients could not continue chemotherapy due to financial constraint. Ten (5.5%) patients died due to bleeding, febrile neutropenia and sepsis during the course of induction therapy. The duration of induction phase was prolonged in many patients due to occurrence of agranulocytosis, thrombocytopenia, altered liver functions and due to lack of proper isolation as well as barrier nursing facilities.

Bone marrow study was done in remaining 157 patients after induction therapy. Out of 157 induction completed patients, 137 (87%) went into complete remission ($<5\%$ blast cells in bone marrow), 14 (9%) into partial remission (5–25% blast cells in bone marrow) and 6 (4%) was not in remission ($>25\%$ blast cells in the bone marrow) (Fig 3).

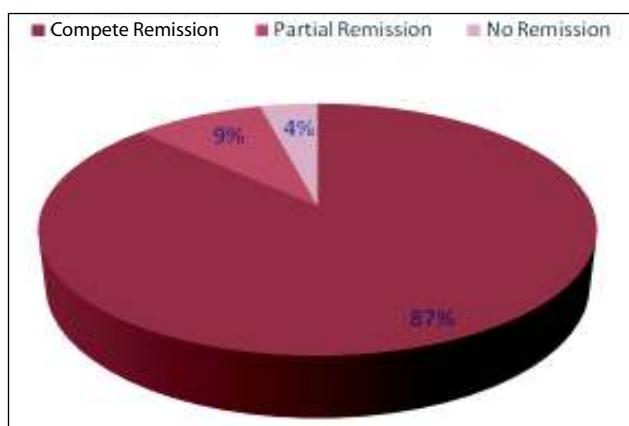


Fig 3. Bone marrow remission pattern after induction therapy (n=157)

Discussion

It is widely accepted that the combination of dexamethasone/prednisolone, vincristine and L-asparaginase is essential for remission induction. The addition of daunomycin appears to be advantageous in high risk patients.^{7,8}

A study by Laningham et al¹³ showed that only 3% of patients had detectable CNS involvement at the time of diagnosis (≥ 5 WBC/ μL with lymphoblasts present). In our study, no patient presented with CNS leukaemia at diagnosis, so we administered only prophylactic intrathecal chemotherapy to all patients.

In comparison to developed countries, the incidence of drop-out of patients was more in our study. This might be due to poverty and misconception regarding outcome amongst our population.

Supportive care of the paediatric cancer patient has played an increasingly important role in the management of these critically ill patients. As intensity of primary treatment has escalated, the side effects such as myelosuppression and infection have also increased.¹⁴

MRC UK ALL X study showed that 2–3% of all patients died during induction or in remission, most frequently due to leucostasis, bleeding or opportunistic infections such as Gram-negative septicaemia and pneumocystis carinii pneumonia.¹⁵ In our study higher incidence of deaths (5.5%) during induction was observed as compared to 2–3% in the above study. It is mostly due to infection as there was lack of facilities for proper isolation and barrier nursing in our country.

According to a study by Silverman et al¹⁶, failure of induction therapy is a relatively rare event occurring in fewer than 5% of children with ALL treated with current regimens, but in our study the failure of induction therapy was 4% which is similar.

Regarding prognosis after induction therapy, a study by Steinherz et al¹⁷ explained that there are occasional patients who demonstrate partial remission ($>5\%$ but $<25\%$ leukaemic blasts) at the end of a standard induction, but in our study the rate of partial remission was a little higher.

Some studies found different predictors for long term outcome of ALL children.^{12,13,15} These predictors include age, WBC count, CNS involvement, gender, leukaemia morphology immunophenotyping, cytogenetics and rapidity to response.¹⁸

A study by Urban et al¹⁹ showed that improved supportive care has decreased the mortality rate during induction therapy to approximately 3% or less. But in spite of adequate supportive care and use of appropriate antibiotics, there is higher incidence of mortality (5.5%) in our patients. This may be due to (a) delayed referral to tertiary care centre, (b) complications of disease at the time of presentation, (c) poor nutrition status, (d) 4-drug induction therapy including daunomycin and (e) higher incidence of nosocomial/community acquired infections due to lack of facilities for isolation and barrier nursing.

In this study we have found that escalated four drug induction therapy causes more myelosuppression and infection during induction therapy, which warrants very strict barrier nursing and isolation. In our study high drop-out during induction therapy has been observed. Availability of drugs at lower cost and supportive social care may improve the condition.

Our study reveals that ALL in children is curable with effective chemotherapy. Poverty, ignorance and misconception regarding outcome are responsible for refusal and discontinuation of chemotherapy in third world countries like Bangladesh. Mortality and morbidity as well as treatment cost can be reduced with the improvement of the facilities for isolation, barrier nursing and supportive treatment and by creating awareness.

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