OUTCOME OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA AFTER INDUCTION THERAPY—3 YEARS EXPERIENCE AT A SINGLE PAEDIATRIC ONCOLOGY CENTRE

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Background: Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. It represents 25% of all childhood cancers and approximately 75% of all cases of childhood leukaemia. A sharp peak of ALL incidence is observed at 2–5 years of age. Objective was to see the bone marrow remission pattern at the end of induction therapy in paediatric ALL patients in our setup. It was a Descriptive case series and conducted at Paediatric Oncology Department, Children Hospital complex Multan from December, 2005 to December, 2008. **Methods**: Thirty-eight paediatric ALL patients were included in the study. Diagnosis was based on history, examination, blast cells count on peripheral blood film and bone marrow biopsy and immunophenotyping on peripheral blood/bone marrow aspirate. According to UK ALL 2003 protocol all patients were given 4-drug induction therapy, i.e., vincristine, prednisolone/dexamethasone, L-aspiragenase and daunomycin. Bone marrow biopsy was repeated at day 28 of induction therapy and remission pattern was seen. **Results:** Out of 38 Patients, 26 (68%) were males. Age range was between 2–12 years (Mean 5.4 years). Bone Marrow Biopsy was done in 38 (100%) and Immunophenotyping in 34 (89%) patients. At day 28 of induction therapy, 28 (74%) patients went into complete remission (<5% blast cells in bone marrow), 2 (5%) into partial remission (5–25% blast cells in bone marrow) and 1 (3%) was not in remission (>25% blast cells in the bone marrow). Seven (18%) patient died due to febrile neutropenia and sepsis during the course of induction therapy. **Conclusion:** ALL in children is curable with effective chemotherapy. Remission can be achieved in most of these patients after induction therapy. However outcome can be improved with effective control of infections.

Keywords: Acute Lymphoblastic Leukaemia, Induction Therapy, Remission.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. It represents 25% of all childhood cancers and approximately 75% of all cases of childhood leukaemia.[1] A 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] At the same time with advent of modern chemotherapy and radiation therapy current event free survival (EFS) rates are approximately 80%.[4–7]

Treatment of children with ALL is divided into 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 show no signs of disease). Usually three-drug induction therapy using vincristine, prednisolone/dexamethasone, plus L-asparagines in conjunction with intrathecal therapy (IT), results in complete remission rates of greater than 95%.[8–10] Patients with increased risk require an anthracycline (e.g., daunomycine). Protocols using this 4-drug combination with intensive consolidation and maintenance therapy uniformly demonstrate improved overall remission duration, even for high- risk patients.[11,12]

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[13–15], while those who fail to attain a complete remission within 4–6 weeks of treatment have particularly dismal prognosis[16]. Half of these patients experience toxic deaths during the induction phase (usually due to infection) and the other half will have resistant disease (persistent morphologic leukaemia) and have poor prognosis.[17] Patient with prognostic or high risk ALL have an improved survival from allogenic stem cell transplantation in first compete remission compared to continued chemotherapy.[18]

This study analyses the results of four-drug induction chemotherapy at paediatric oncology department of Children Hospital Complex Multan.

PATIENTS AND METHODS

It was a descriptive study conducted at paediatric Oncology Department of Children Hospital Complex Multan from December 2005 to December 2008.

Thirty eight newly diagnosed patients of paediatric ALL were included during this period. Patients who had relapsed ALL, infantile leukaemia,

ALL with L3 morphology (Burkett's Type), and who were given chemotherapy elsewhere, were excluded from the study. Patients were admitted in the oncology ward for the whole duration of induction therapy.

After history and clinical examination, CBC, electrolytes, liver, renal function test, tumour lyses profile, blood culture, CSF & chest X-Ray. Peripheral blood film and bone marrow biopsy/aspirate were seen for detection of blasts cells. Immunophenotyping by flow cytometery was done on peripheral blood sample or bone marrow aspirate.

Patients were stabilized haemodynamically by given packed cells transfusion if Hb <8 G/dl, platelets transfusion if platelet counts <20,000/mm.[3] Tumour lyses prophylaxis was started in the form of adequate hydration, allopurinol, phosphate binder and treatment of hyperkalemia and hypocalcaemia where needed. For fabrile neutropenia (ANC $<1.0\times10^9$/L plus fever ≥38 ºC (100.4 ºF) for >4 hours or single spike of ≥38.5 ºC (101.3 ºF), ceftazidine 100 mg/kg/day in 3 divided doses and Amikacin 15 mg/kg/day in two divided doses were started. Meropenum was started in resistant infections. Amphotericin B was added after 5–7 days if fever did not settle.

According to UKALL 2003 protocol regimen B, four-drug induction therapy with vincristine, dexamethasone/prednisolone, L-Asparaginase and Daunomycin was started. Intrathecal cytarabine was given on day 1 and intrathecal methotrexate on day 8 and day 28.

Bone marrow biopsy was repeated to see the end of induction response, i.e., remission on day 28. Remission pattern was noted whether complete remission (<5% blasts cells in the bone marrow, M1), partial remission (5–25% blast cells, M2) or no remission (>25% blast cells, M3).

RESULTS

Out of 38 patients, 26 (68%) were males and 12 (32%) females. Age range was from 2–12 years (Mean age 5.4 years).

Pallor was noted in 32 (84%), fever in 28 (73%), hepatospleenimegaly in 33 (86%) and lymphadenopathy in 22 (57%) patients.

TLC was <50,000/mm^3 in 28 (73%) and >50,000 in 10 (27%) patients. Haemoglobin was in the range of 6–10 G/dl in most of the cases. Blast cells were detected in 36 (94%) patients on peripheral blood film with range of 2% to 96% and 38 (100%) patients on bone marrow biopsy/aspirate. Immunophenotyping was done in 34 (89%) patients. It showed Pre-B cell ALL in 31 (91%) and pre-T cell ALL in 3 (9%) patients. Immunophenotyping was not done in 4 (11%) patients due to financial problem.

Mediastinal mass was detected in 3 (8%) patients on X-ray chest (Table-1).

Seven (18%) patients died during course of induction therapy mainly due to febrile neutropenia and sepsis, despite appropriate antibiotic cover and supportive care. Day 28 bone marrow biopsy was done in remaining 31 patients. Twenty-eight (74%) patients went into complete remission, i.e., M1 marrow morphology, 2 (5%) patients were in partial remission, i.e., M2 marrow and 1 (3%) patient did not go into remission, i.e., M3 marrow (Table-2).

Table-1: Patient Characteristics & Diagnostic Parameters (n=38)

Characteristics	Patients
Age (Years)	
Range	2–12
Mean	5.4
Sex	
Males	26 (68%)
Females	12 (32%)
Presentation	
Pallor	32 (84%)
Fever	28 (73%)
Hepatospleenomegaly	33 (86%)
Lymphadenopathy	22 (57%)
Mediastinal Mass	3 (8%)
WBC Count	
<50,000 / µL	28 (73%)
>50,000 /µL	10 (27%)
Blast cell found on peripheral film	36 (94%)
Blast cell count (Range)	2–96%
Blast cells found on bone marrow biopsy	38 (100%)
Immunophenotyping Done	34 (89%)
Pre-B cell ALL	31 (91%)
Pre-T cell ALL	3 (9%)
Blast Cells in CSF	0 (0%)

Table-2: Bone marrow remission pattern at day 28 of induction therapy (n=38)

Remission Pattern	No. of Patients
Complete Remission	28 (74%)
Partial Remission	2 (5%)
No Remission	1 (3%
Patients expired during induction	7 (18%)

DISCUSSION

The major therapeutic breakthrough in childhood ALL was achieved by the use of a multi drug induction regimen and effective mainly CNS-directed therapy in combination with intensified supportive care. It is widely accepted that the combination of prednisolone, vincristine and L-aspiragenase is essential for remission induction. The addition of daunomycine appears to be advantageous even though there are very few controlled studies which addressed this issue.[19,20]

Researchers affiliated with European AIEO-BFM ALL 2000 Trail have reported that dexamethasone in the induction regimen for childhood acute lymphoblastic leukaemia reduces the relapse rate compared to prednisolone.[21] The above results were in contrast to a study presented by researches affiliated with EORTC Trial 5895 who found no difference between dexamethasone and prednisolone in the

induction regimen.[22] It should be noted the dose of dexamethasone in the AIE-BFM trial was 10 mg/m^2 compared to 6 mg/m^2 in the EORTC study, while the dose of prednisolone was same in both studies.

There is a tendency towards a higher incidence of notable complications in the DEXA Arm than in the PRED Arm. Hurwitz *et al*[23] described and increased incidence of Gram-Negative bacteremia and induction death in a group of patients who received DEXA during induction compared with historical controls who received PRED. This was not seen in the CCG 1922 study, which used a three-drug induction schedule (No Anthracycline).[24] In our study, in four-drug induction regimen, prednisolone was given to 6 (16%) and dexamethasone was given to 32 (84%) patients. One (3%) in prednisolone and 6 (16%) patients in dexamethasone group expired due to sepsis. So our results correlate with above study, as sepsis was more frequently observed in DEXA patients than in PRED patients. It should be noted that this was in the context of a 4-drug mylosuppressive induction schedule including anthracycline (Daunomycine).

A study by Laningham FH *et al* showed that only 3% of patients have 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 gave only prophylactic intrathecal chemotherapy to all patients. Intrathecal cytarabine was given on day 1, and intrathecal methotrexate on day 8 and 28. Patients with CNS involvement at diagnosis are treated with intrathecal therapy and subsequent radiation. Unless specific therapy is directed towards the CNS, 50% to 70% or more of children will develop overt CNS leukaemia.[25]

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 so have the side effects such as mylosuppression and infection.[26]

MRC UK ALL X study showed that 2–3% all patients will die during induction or in remission, most frequently due to leucostasis, bleeding or opportunistic infections such as gram-negative septicaemia and pneumocystic carinii pneumonia.[27]

In our study higher incidence of deaths, i.e., 18% during induction was observed as compared to above studies, i.e., 2–3%. All of these 7 (18%) patients expired due to severe sepsis in spite of good antibiotic coverage. In these patients infection sites were low respiratory tract in 4 and urinary tract in 2 patients. In 1 (3%) patient site of infection could not be detected.

According to a study by Silverman LB *et al*[18], failure of induction therapy is a relatively rare event occurring in fewer than 5% of children with ALL treated with current regimens. Induction failure occurs when the patient demonstrate residual leukaemia in the end of induction phase bone marrow aspirate (typically performed on day 28 or 36 depending on regimen). The overall event free survival for these patients is only 16%.[11]

Pui CH *et al* described the new definition of remission as M1, M2 and M3, after induction therapy.[28] Regarding prognosis after induction therapy, a study by Steinherz *et al* explained that there are occasional patients who demonstrate M2 marrow (>5% but <25% leukaemic blasts) at the end of a standard induction. Although many of these patients will eventually go into remission (either with and extension of the standard induction or with institution of more intensive treatments), this slow response to initial therapy is indicative of poor prognosis.[29]

A study by Urban C *et al* showed that improved supportive care has decreased the mortality rate during induction therapy to approximately 3% or less.[30] But in spite of adequate supportive care and use of appropriate antibiotics, there is higher incidence of mortality in our patients, i.e., 18%. 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 daunomycine (e) use of dexamethasone and (f) higher incidence of nosocomial/community acquired infections.

CONCLUSION

ALL in children is curable with effective chemotherapy. Remission can be achieved in most of these patients after induction therapy with UKALL 2003 protocol regimen. In our setup, there is quite higher incidence of mortality as compared to international data. However this mortality rate may be decreased with early referral and further improvement in control/treatment of infections. This may be achieved by proper barrier nursing and better choice of appropriate antibiotics during induction therapy.

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