ORIGINAL ARTICLE
RESPONSE RATE OF PAKISTANI CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA TO MEDICAL RESEARCH COUNCIL ACUTE LYMPHOBLASTIC LEUKAEMIA 97 CHEMOTHERAPY PROTOCOL

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Background: Acute lymphoblastic leukaemia (ALL), a malignancy of lymphoid lineage cells, has excellent prognosis in children. In Pakistan, a few studies highlighted the response of ALL to chemotherapy. The Present study was planned to see the response rate of Pakistani children with ALL to Medical Research Council ALL 97 (MRCALL97) chemotherapy protocol. This descriptive case series was conducted at the Department of Haematology, Armed Forces Institute of Pathology and the Department of Paediatric Oncology, Combined Military Hospital, Rawalpindi from 16th of February 2007 to 16th of August 2007. **Methods**: Diagnosed children with ALL fulfilling the inclusion criteria were interviewed regarding history of the present, past illnesses, and family history. Physical examination was performed. Presenting clinical features, blood counts and blood and bone marrow blasts percentage were used to see the response on day 29 post chemotherapy. The data was recorded on a structured proforma for statistical analysis. **Results:** A total of 33 patients were studied including 26 males and 7 females. Twenty-five patients belonged to age group 2–9 years, and 8 to <2 or >9 years, median age being 4.5 years. Presenting WBC count was $<50\times10^9$/L in 30 patients and $>50\times10^9$/L in 3 patients. At the end of induction, complete remission was achieved in 31 out of 33 (94%) patients while two patients did not achieve remission. **Conclusion:** Response rate of Pakistani children with ALL to chemotherapy was superior to the previously reported figures from Pakistan.

Keywords: Acute Lymphoblastic Leukaemia, ALL, remission, chemotherapy

INTRODUCTION

Acute lymphoblastic leukaemia (ALL), the most common cancer diagnosed in childhood, with higher incidence for white than for black.[1] In Pakistan, studies have been conducted on different aspects of acute leukaemia.[2–5] It is a malignancy of haemopoietic progenitor cell consisting of an expanding clone of neoplastic cells infiltrating blood and bone marrow.[6] Bone marrow shows >20% blast cells.[7] It is more common in the paediatric age group.[8] Chemotherapy of ALL aims at effecting a cure by combination of different drugs given in the form of cycles. Better understanding of leukaemic cell biology, discovery of more accurate diagnostic techniques and the advent of newer and relatively safer chemotherapeutic agents has tremendously improved the treatment outcome.[9,10]

There remains a substantial minority of patients who suffer disease relapse despite falling within an apparently 'standard risk' category. A greater proportion of relapse cases arise out of this apparently low risk group than from the high risk which comprises only 10–12% of new cases.[3] Identification of this intermediate risk sub-group include monitoring early response to therapy which has traditionally been done by morphological assessment of marrow or peripheral blood blast count after 7–14 days of induction chemotherapy with presence of gross residual leukaemia identifying patients at increased risk of relapse.[11]

Presence of Minimal Residual Disease (MRD) to a level of greater than 1 leukaemic cell in 10,000 normal cells detected by sensitive molecular or immunological techniques at the end of induction, or later, may provide a more sensitive method for identifying such patients, selecting them for treatment on high risk protocols containing alternative treatment strategies including bone marrow transplantation.[12]

Medical Research Council Acute Lymphblastic Leukaemia 97 (MRCALL97) protocol was started in the late 90s. It comprises sequential administration of chemotherapeutic agents in a specific manner. In Pakistan, most of the published work mainly focused upon epidemiological and other aspects of acute lymphoblastic leukaemia.[2–4,13–19] A few studies were also conducted on response to chemotherapy.[20–24] The MRCALL97 chemotherapy protocol is being practiced in various centres in our country but its results have not been documented. The present study was planned with a view to see the response rate of Pakistani children to this protocol. The study was restricted to remission induction phase only.

PATIENTS AND METHODS

This study was conducted at Department of Haematology Armed Forces Institute of Pathology, Rawalpindi in collaboration with the Department of Paediatric Oncology, Combined Military Hospital,

Rawalpindi Pakistan, from 16th February 2007 to 16th July 2007 over a period of 6 months on 33 Pakistani children, both males and females and aged <15 years with newly diagnosed acute lymphoblastic leukaemia. Children migrated from other countries and temporarily residing in Pakistan, >15 years of age, already receiving some sort of chemotherapy for acute lymphoblastic leukaemia, and children with critical co-morbid conditions making chemotherapeutic intervention impracticable were excluded from the study.

After an informed written consent, a detailed relevant history of present, past illnesses and family history was taken. Physical examination was done next with main focus on haematopoietic system. Blood counts and bone marrow examination was performed starting the chemotherapy. The findings of history, physical examination, blood and bone marrow examination were recorded on a proforma. The diagnosis of ALL was established on the basis of morphology, cytochemistry and immunophenotyping wherever necessary. Risk stratification at the start of treatment was done on the basis of gender, age of the patient, presenting white blood cell count and morphology of blast cells. High risk was considered with male gender, age <2 and >9 years, presenting WBC count of $>50 \times 10^9$/L, FAB ALL-L2 or L3 morphology and T-cell ALL morphologically and on cytochemistry. Subsequent risk stratification was done on the basis of response to therapy during the 1st and 2nd weeks of treatment. Patients received supportive treatment before the start of chemotherapy. Outcome was measured by clinical improvement (disappearance of symptoms and signs) as well as normalisation of haemoglobin, white blood cell and platelets counts, and disappearance of blast cells from blood and bone marrow. Bone marrow examination was performed as per recommendations of the protocol under study. Response rate was recorded in the form of complete remission or no remission on day 29 of induction phase chemotherapy.

Data was analysed using SPSS-15. Percentage of patients showing complete remission or no remission was calculated. Mean and standard deviation were calculated for the numerical variables like white blood cell counts at presentation and on remission induction.

RESULTS

A total of 33 patients were studied, 26 (79%) males and 7 (2%) females. Male to female ratio was 3.7:1. Median age of the patients was 4.5 years (range: 6 months to 13 years). Among the clinical features (Table-2), fever and pallor was seen in all the patients (100%) at presentation. At the end of remission induction fever was seen in 1 out of 33 patients (3%) and pallor in 6 out of 33 patients (18%). Bone pain was seen in 9 out of 33 patients (27%) at presentation and none at the end of remission induction. Bleeding manifestations (gum bleeds, epistaxis, patechae and ecchymoses) were seen in 18 out of 33 patients (54%) and none at the end of remission induction. Organomegaly (lymphadenopathy, splenomegaly and hepatomegaly) was seen in all the patients at presentation and 2 out of 33 (6%) patients at the end of remission induction therapy (Table-2).

Haematological parameters are shown in Tables-3 and 4. Mean haemoglobin was 7.1±0.8 g/dL on day zero. At the end of remission induction, it was 10.6±1.5 g/dL in 31 out of 33 patients (94%) and 8.5±0.5 g/dL in the remaining 2 patients (6%). Platelet count at presentation was $39\pm31\times10^9$/L. At the end of remission induction it was $309\pm164\times10^9$/L in 31 out of 33 patients. One out of the remaining two patients had platelet count of 33×10^9/L while the other had 80×10^9/L platelets. White blood cell count was $32\pm24\times10^9$/L at presentation. At the end of remission induction white blood cell count was $8.3\pm3.7\times10^9$/L in 31 out of 33 patients. In the remaining two patients it was 13.5×10^9/L and 5.3×10^9/L respectively. Mean percentage of blast cells in peripheral blood was 66% at presentation. At the end of remission induction, blast cells disappeared from the blood in 31 out of 33 patients. Out of the remaining 2 patients, one had 8% blast cells, while the other had 90% blast cells in peripheral blood.

Bone marrow examination at presentation revealed depression of all the three cell lines in 30 out of 33 patients showing 90–94% blast cells. Diluted marrow was seen in the remaining 3 patients showing 54 to 88% blasts cells. At the end of remission induction therapy, bone marrow examination in 27 patients revealed normal cellularity with recovery of all the 3 cell lines. Four patients had mildly hypocellular marrow with mild depression of haemopoiesis. Out of the remaining 2 patients one had 15% blast cells while the other had 90% blast cells in the bone marrow.

Two patients had FAB ALL-L2, while 31 patients were found to have FAB All-L1 morphology. Among ALL-L1 patients, 5 had T-Cell ALL (on morphology and cytochemistry). No patient of ALL-L3 was seen in this study. Five patients were placed in the high risk group, 8 in the intermediate risk group and 20 patients had standard risk disease.

Table-1: Age of patients and remission status on day 28 (n=33)

Age (Years)	Number	Percentage	Complete remission	No remission
>2<9	25	76 %	31	2
<2>9	8	24 %	(94.0%)	(6.0%)

Table-2: Clinical parameters on day 0 and 28 (n=33)

Parameter	Day 0 (n=33)	Day 28 Remission (n=31)	Day 28 No remission (n=2)
Fever	33 (100 %)	0	1 (50%)
Pallor	33 (100 %)	6 (18 %)	2 (100%)
Bleeding	18 (54 %)	0	0
Organomegaly	33 (100 %)	0	2 (100%)
Bone pain	9 (27 %)	0	0

Table-3: White blood cell count on day 0 (n=33)

White Blood Cells ×10⁹/L	Number	Percentage
<50	30	91.0
>50	3	9.0

Table-3 header renders as: White Blood Cells $\times 10^9$/L.

Table-4: Haematological parameters of patients

Parameter	Day 0 Mean±SD	Day 28 Mean±SD
Haemoglobin g/dL	7.1±0.8	10.6±1.6
White blood cell count ×10⁹/L	32±24	8±3.7
Platelet count ×10⁹/L	39±31	309±165
Blood blasts %	66±12	3±2
Marrow blasts %	9±4	3±2

White blood cell count $\times 10^9$/L; Platelet count $\times 10^9$/L.

DISCUSSION

Contemporary risk-directed therapy has advanced the cure rate for childhood acute lymphoblastic leukaemia to near 80%. Molecular genetic analyses of leukaemic cells, pharmacodynamic studies of antileukaemic agents, and pharmacogenetic studies of the host's drug-metabolising enzymes, drug transporters, and drug targets are providing a rational base for further improvement of treatment efficacy and the reduction of complications. Early treatment response, as defined by the measurement of minimal residual disease, which reflects both the drug responsiveness of leukaemic cells and host pharmacodynamics/pharmacogenomics, is the most reliable prognostic indicator for gauging the intensity of treatment. A study conducted from 1991 to 1995 on 1200 children aged 0–15 years showed complete remission induction of 96.5%.[25] Silverman *et al* found complete remission induction (CR) in 98.2% patients 0–18 years of age.[26] These studies were carried out on larger number of patients. The present study has been conducted on 33 patients only and complete remission was seen in 93.5% patients. These results are different from the above mentioned studies

In Pakistan, some of the previously conducted studies have shown variable results. The majority of the previous research focused upon non therapeutic aspects of acute leukaemia.[2–4,12–19] Some of the studies were conducted on treatment outcome of different chemotherapy regimens in children as well as adults having acute lymphoblastic or acute myeloblastic leukaemia.[21–24] In a study conducted at Armed Forces Bone Marrow Transplant Centre Rawalpindi, FLAG-IDA was found to be effective in relapsed or refractory anaemia.[22] Treatment outcome of adult acute lymphoblastic leukaemia was studied in 2003 and it was found that the results were comparable to those already reported in literature.[15] Similar results were reported by another study conducted on long term outcome of acute myeloid leukaemia.[23]

In a study with the main objective to compare the outcome results of two protocols, UKALL-X and BFM for the treatment of ALL, first 27 patients were treated with the protocol UKALL-X and next 38 patients were treated with the modified BFM protocol.

Induction remission was seen in 85% of patients on UKALL-X and 86.6% of patients on BFM protocol.[24] Results of the present study are different from this study as well as from those of an earlier study which was conducted on treatment of childhood ALL at AFIP during 1996–97.[24] This study aimed at comparing the two popular chemotherapy trials of childhood ALL, i.e., United Kingdom acute lymphoblastic leukaemia X (UKALLX) and UKALLXI trials in Pakistani children. UKALLX was found to be better trial as it was better tolerated and carried lesser toxicity. Although seeing remission at the end of induction phase was not the primary aim of this study, it is mentioned in its results that all the patients went into remission and 3 out of 27 patients died during the study, having a mortality rate of about 11%. Thus we can say that, practically complete remission was seen in 89% patients. Regarding clinical features of patients, fever and pallor was seen in all the patients at presentation. Lymphadenopathy and/or hepatosplenomegaly were also seen in all the patients. These findings are in accordance with those reported previously.[18]

The results of our study are better as no mortality was seen and complete remission was observed in 94% of patients. The reason could be better drug combination, improved diagnostic techniques or better risk stratification. However this study was carried out on a small sample and was restricted to remission induction phase only. It is not appropriate to formulate any guidelines on the basis of its results. Therefore further studies on larger scale would be highly appreciated in this regard.

CONCLUSION

The response rate of childhood ALL to MRCALL97 chemotherapy protocol was superior to the previously reported response rates to different chemotherapy protocols from Pakistan. However it was inferior to the internationally reported figures.

RECOMMENDATIONS

It is recommended that more studies should be conducted on larger number of patients to see the response rate of Pakistani children to different chemotherapy protocols so as to select the one which is most effective and least toxic.

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