Bangladesh Med Res Counc Bull 2012; 38: 43-46

Outcome of adult acute lymphoblastic leukaemia following induction chemotherapy with modified MRC UKALL XII/ECOG E2993 protocol

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Abstract

Cure rates for adult acute lymphoblastic leukaemia (ALL) in developing countries are significantly lower because of problems unique to these countries. Recent studies have reported complete response rates for any induction regimen of more than 90% in adult ALL patients. This study was conducted to evaluate the response rate of induction chemotherapy in adult ALL patients in the Department of Haematology, Bangabandhu Sheikh Mujib Medical University, from January 2007 to December 2008. In this observational study, 35 newly diagnosed ALL patients classified either as L1/L2 according to French-American-British (FAB) classification, aged between 15 to 60 years were assigned for induction therapy with modified MRC UKALL XII/ECOG E2993 protocol. But ultimately 30 patients completed therapy and available for statistical analysis. Among the studied 30 cases 12(40%) patients after phase 1 and overall 24(80%) patients after phase 2 induction therapy, achieved morphologic complete remission (CR). After phase 2 therapy 6(20%) patients fell in the group of non responders (NR) as the blast percentage was ≥5% at the time of bone marrow evaluation. This study shows the response rates in adult ALL with induction therapy slightly below the anticipated response rates of developed countries which may be due to little modification of the original protocol.

Introduction

Acute lymphoblastic leukaemia (ALL) is a heterogeneous group of disorders that result from the clonal proliferation and expansion of malignant lymphoid blast cells in the bone marrow, blood and other organs. It vary with respect to the morphologic, cytogenetic, molecular, and immunologic features of the neoplastic cells[1-3].

Contemporary ALL treatment programmes include induction, intensified consolidation, maintenance phases and central nervous system (CNS) prophylaxis that accompanies induction and consolidation[1-10]. The goal of remission induction therapy is haematologic complete remission (CR), as defined by the eradication of morphologically detectable leukaemic cells in blood and bone marrow that is eradication of more than 99 percent of the initial burden of leukaemic cells and the return of normal haematopoiesis and a normal performance status[3,4,9].

Advances in ALL therapy have led to long-term survival rates of >80% in children. However, only approximately 30-40% of adults achieve long-term disease-free survival[3]. Standard induction of remission of adult ALL includes at least a glucocorticoid, vincristine, an anthracycline and L-asparaginase while intrathecal methotrexate is used for CNS prophylaxis[5,7-9]. However, CNS prophylaxis can consist of intrathecal chemotherapy, high-dose systemic chemotherapy and craniospinal irradiation (XRT)[2,8,11].

The large international MRC UKALL XII/ECOG (Medical Research Council in the United Kingdom and Eastern Cooperative Oncology Group) E2993 study reported a complete remission rate of 91% for 1521 adult patients irrespective of risk assessment with a standard induction regimen consisting of phase 1 therapy with vincristine, prednisolone, daunorubicin and L-asparaginase and phase 2 therapy with cyclophasphamide, cytarabine and 6-Mercaptopurine including central nervous system (CNS) prophylaxis and treatment of CNS disease. The same study showed that a complete remission rate of 97% in 533 adults at standard risk[5,6]. In the future, an increase of molecular CR rates i.e., level of minimal residual disease after induction therapy below the detection limit of clone-specific polymerase chain reaction (PCR) may be the most important goal and measure for efficacy of induction therapy[8].

Cure rates for adult ALL in developing countries like Bangladesh are significantly lower because most of the patients have to face different problems in getting proper treatment. One study in a resource-constrained setting showed that at least

15% of patients after successful induction abandoned the treatment because of financial constraints, prolonged travel time to treatment facility and switching over to alternative medicines[12].

At present, there is no data available in Bangladesh on the rate of cytomorphologic CR after induction therapy in adult ALL or on other study with the original or modified MRC UKALL XII/ECOG E2993 protocol. The main aim of this study was to evaluate the response rate of induction therapy in adult ALL patients in Bangabandhu Sheikh Mujib Medical University (BSMMU) with modified MRC UKALL XII/ECOG E2993 protocol. Two modifications (reduction of dose of daunorubicin from 60 mg/m^2 to 40 mg/m^2 in phase 1 and omission of 6-mercaptopurine in phase 2) have been done in induction therapy to reduce toxicity of chemotherapy[13,14]. To reduce the risk of CNS relapse the number of intrathecal methotrexate in phase 1 of induction therapy has been increased to four (day 1, 8, 15, 22) instead of single dose (day 15)[13]. This modification has been considered in context of our compromised supportive care, and patient's compliance and affordability. Another aim of this study is to correlate the outcome with the initial clinical-haematological characteristics of the patients.

Materials and Methods

In this observational study, thirty five newly diagnosed adult ALL patients between 15 to 60 years of age classified either as L1/L2 (FAB classification) were assigned. The study was carried out in the Department of Haematology, BSMMU from January 2007 to December 2008. Out of 35 patients 5 were dropped; 2 because of early death, and 3 due to resistant disease and remaining 30 were ultimate study sample.

Relevant clinical data including laboratory findings were recorded with written consent. Peripheral blood film (PBF) examination (Leishman stain), estimation of Hb (cyanmethaemoglobin method), complete blood count from PBF, bone marrow examination (Leishman stain), cytochemistry (PAS & MPO) by commercially available kit (Sigma kit) were done for diagnosis of the disease and CSF study was done to detect CNS involvement. Cytogenetic study and cell markers were not performed due to lack of facility. For pre-induction evaluation, liver function tests, kidney function tests, serum electrolytes, lactate dehydrogenase (LDH), uric acid, random blood sugar were done by autoanalyzer (Dade Behring, model RXL Max); coagulation assay was done by fully automated coagulometer (Sysmex, model CA-500) & by latex agglutination method. Routine examination of stool & urine, ECG, X-ray chest were also done. All study population received induction therapy with modified MRC UKALL XII/ECOG E2993 protocol (Table I).

Table I: Induction therapy: Modified MRC UKALL XII/ECOG E2993

Phase and therapy	Dose	Route	Schedule (day)
Phase 1, weeks 1-4			
Daunorubicin	40 mg/m^2	IV	1, 8, 15, 22
Vincristine	1.4 mg/m^2	IV	1, 8, 15, 22
L-asparaginase	7000 U/m^2	IV or IM	17-28
Prednisone	60 mg/m^2	PO	1-28
Methotrexate	12.5 mg	IT	1, 8, 15, 22
Phase 2, weeks 5-8			
Cyclophosphamide	650 mg/m^2	IV	1, 15, 29
Cytarabine	75 mg/m^2	IV	1-4,8-11,15-18,22-25
Methotrexate	12.5 mg	IT	1, 8, 15, 22

IV indicates intravenously; IM, intramuscularly; PO, by mouth; IT, intrathecally

Patients with CNS involvement were treated by intrathecal triple chemotherapy (methotrexate 12.5mg, cytarabine 30mg, corticosteroids 40mg) weekly for 16 times. G-CSF was used for early peripheral recovery of neutrophils. Full blood count was done at 3-day interval until the recovery of peripheral blood count. Bone marrow examination was done after phase 1 at day 28+ and after phase 2 therapy with the peripheral recovery to assess remission status. Morphologic CR was assumed by <5% blast cells in the bone marrow with no peripheral circulating blasts, platelets >100 x10^9/L, an absolute neutrophil count >1.5x10^9/L and Hb level >10gm/dl. Patients who did not achieve CR after phase 2 therapy considered as non responders (NR) or resistant cases.

Precautions were taken to minimize the risk of infection. Patients with fever were treated with broad-spectrum antibiotics and anti fungal agents. Platelet or fresh frozen plasma transfusion were given to patients with the evidence of bleeding. A haemoglobin level >8 gm/dl was generally maintained by transfusion of red cells concentrate.

Statistical analysis was done using SPSS 17.0. The characteristics of the patients and their response to treatment were compared by chi-square test for univariate analysis. *P* value less than 0.05 was considered as significant.

Result

Sex, age, WBC count, Hb level, platelet count, percentage of peripheral blood and bone marrow blasts, FAB classification & clinical characteristics at presentation of 30 patients are summarized in Table II. The mean age of the patients was 28.07 years (Range: 15- 60 years; SD: ±12.31). Out of 30 cases 22 were male (73%) and 8 were female (27%) giving a male to female ratio of 3:1.

Table II: Clinical-pathologic characteristics of 30 adults with ALL

Characteristics	Value
Clinical features	
Mean age, years (range)	28.07 (15-60)
M/F	22/8
Lymphadenopathy (%)	18 (60)
Splenomegaly, 2 cm or larger (%)	18 (60)
Mediastinal mass, chest X-ray (%)	12 (40)
Hepatomegaly, 2 cm or larger (%)	11 (37)
CNS (%)	2 (7)
Laboratory data	
Blast count range, %	
BM	41-100
PB	0-100
Mean WBC count, $\times 10^9$/L (range)	52.78(2.0-250.0)
Mean hemoglobin level, g/dL (range)	8.31 (4-12)
Mean platelet count, $\times 10^9$/L (range)	76.83(10.0-240.0)
Morphologic features, FAB, n=30	
L1	9
L2	18
NA	3

BM indicates bone marrow; PB, peripheral blood; and NA, not applicable.

Anaemia (Hb level ≤10 gm/dl) was present in 63% of patients, WBC count ≥30X10^9/L in 43% of patients, thrombocytopenia (platelet count ≤100 x10^9/L) in 73% of patients and 63% patients had ≥ 90 % blasts in the bone marrow.

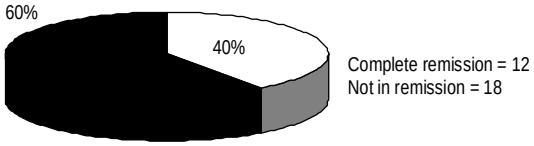

Fig.1: Distribution of the patients by outcome of phase 1 therapy (n=30)

Statistical analysis was performed taking into account of clinical-pathological characteristics of 30 cases. Out of 30 patients, 12 patients achieved CR after phase 1 therapy (Fig.1). Presenting WBC count and lymphadenopathy (Table III) were found to have significant influence (P<0.05) on the achievement of CR.

Table III: Univariate analysis on CR achievement after phase 1 therapy

Variable	Criteria	% CR	P-value
Age	<30 yrs vs ≥30 yrs	48 vs 22	0.193
Sex	M vs F	45 vs 25	0.312
Lymphadenopathy	+ vs -	22 v 67	0.015*
Splenomegaly	+ v s-	44 vs33	0.543
Mediastinal mass	+ vs -	33 vs 44	0.543
Hepatomegaly	+ vs -	45 vs 37	0.643
WBC count	<30×10^9/L vs ≥30×10^9/L	59 vs 15	0.016*
Hb level	≤100 g/L vs >100 g/L	32 vs 55	0.216
Plt count	≤100×10^9/L vs >100× 10^9/L	32 vs 63	0.129
FAB	L1 vs L2	44 vs 39	0.933
Blast % in BM	>90 vs ≥90	55 vs 32	0.216

*=P value <.05 is significant

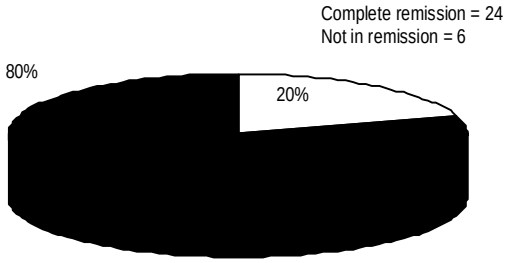

Fig.2: Distribution of the patients by outcome of phase 2 therapy (n=30)

Out of 30 patients, 24 patients achieved CR after phase 2 therapy (Fig. 2). By univariate analysis (Table IV), statistical significance on achievement of CR was found for sex (male/female; P=0.013), age (<30 years; P=0.028), WBC count (<30x10^9/L; P=.027), Hb level (>10 mg/dl; P=0.037) and percentage of blast in the bone marrow (<90%; P= 0.037).

Table IV: Univariate analysis on CR achievement after phase 2 therapy

Variable	Criteria	% CR	P-value
Age	<30 yrs vs ≥30 yrs	90 vs56	0.028*
Sex	M vs F	99 vs50	0.013*
Lymphadenopathy	+ vs-	72v92	0.192
Splenomegaly	+ vs-	89 vs67	0.136
Mediastinal mass	+ vs -	83 vs 78	0.709
Hepatomegaly	+ vs -	82 vs 79	0.850
WBC count	<30×10^9/L vs ≥30×10^9/L	94 vs62	0.027*
Hb level	≤100 g/L vs >100 g/L	68 vs 100	0.037*
Plt count	≤100×10^9/L vs >100×10^9/L	77 vs13	0.536
FAB	L1 vs L2	89 vs 72	0.392
Blasts % in BM	<90 vs ≥90	100 vs 68	0.037*

*= P value < .05 is significant

Discussion

Acute lymphoblastic Leukaemia, the most common childhood acute leukaemia, represents about 80% of acute leukaemias; however, it makes up only 20% of adult leukaemias. ALL has an overall incidence of 1 to 1.5 per 100,000 persons and a bimodal distribution. The median age of patients with ALL in most registry studies is between 25 and 35 years[2].

The clinical-pathological characteristics of 30 adult ALL patients are more or less similar to studies in different countries[14] including Bangladesh[15] except sex distribution, male patients (22/30 or 73%) were greater than female patients (8/30 or 27%) which is more or less similar to a study in Bangladesh[15]. But this is in contrast with the observation of Luciana Annino et al.[14] who found male 59% versus female 41%. The higher incidence of ALL among males in our study may be due to female patients being neglected more and get less opportunity to attend a tertiary medical centre.

In this study among 30 patients, 12(40%) patients after phase 1 and overall 24(80%) patients after phase 2 of induction therapy achieved morphologic CR. The remaining 06(20%) patients though

responded initially, ultimately fell in the group of non responders (NR) as the blast percentage was ≥5% at the time of bone marrow evaluation. This result is slightly lower than the original study by Jacob et al.[5] who found 91% CR, following induction therapy with original MRC UKALL XII/ECOG E2993 protocol. This small difference in CR rate may be due to small sample size or interruption in the continuation of induction therapy caused by toxicities of chemotherapy in few cases or poor supports especially during therapy or little modification of chemotherapy protocol. But modified MRC UKALL XII/ECOG E2993 protocol used in this study is comparable to other standard induction teatment protocol for ALL[13,14]. However the clinical-haematological features might also have influenced the response rate.

Univariate analysis showed a significant influence on achievement of CR for lymphadenopathy (absence doing better) and WBC count at presentation ($<30\times10^9$/L) after phase 1 and sex (males doing better), age (<30 years), WBC count ($<30\times10^9$/L), Hb level and blast percentage in the bone marrow (<90%) after phase 2 therapy but not for platelet count, mediastinal mass, splenomegaly and hepatomegaly. Antonella Vitale et al.[1] reported an impact on achievement of CR on sex (male/female; P=.004), age (<30 years; P=.04), WBC count ($<30\times10^9$/L; P=.02) and lymphadenopathy (P=.06).

Remission induction of adult ALL patients with intensive chemotherapy using different protocols have shown more or less similar result worldwide. The aim of the induction therapy is always to achieve a better CR rates while minimizing therapy related toxicities, thus reducing morbidity and mortality. The standard induction therapy used in this study resulted in a response rates slightly below the anticipated response rates of developed countries which may be due to prolongation of duration of therapy, poor supports especially during the period of pancytopenia, lack of molecular prognostic markers identification and advanced treatment options or due to little modification of the original protocol. Considering all these settings the response rates of induction therapy used in this study is satisfactory. So this study may have significance for the development of local capacity based effective treatment protocol for ALL in our country. However further large scale randomized study with a long term follow-up should be undertaken to ascertain the success of induction therapy in adult ALL.

Acknowledgement

We express our gratitude to all patients who were incorporated in this study.

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