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Treatment-related Complications in Childhood Acute Lymphoblastic Leukemia: Results of Medical Research Council UKALL X

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid neoplasms resulting from the proliferation of malignant lymphoid cells. The aim of this study was to evaluate treatment-related complications in children with ALL receiving the Medical Research Council (MRC) UKALL X protocol.

Methods: In this retrospective cross-sectional study, children with ALL receiving the MRC UKALL X protocol from 2008 to 2015 in Bahrami University Hospital, Iran, were enrolled. The clinical and morphological features were analysed and treatment-related complications were assessed.

Results: Out of 67 children with ALL receiving the MRC UKALL X protocol, 44 (65.6 %) were boys and 23 (34.4%) were girls. Seven patients (10.7%) relapsed in the three years of diagnosis, and 50 children (74.6%) had an overall survival of three years. Average age in three-year-survival group and mortality group was 6.92 (SD: 3.96) and 6.35 (SD: 7.47), respectively (P= 0.38).

Conclusion: Overall survival and relapse rates in this study confirm that this protocol is an appropriate treatment strategy.

Keywords: Acute lymphoblastic leukemia (ALL), Mortality, MRC UKALL X, Neutropenia, Pediatric

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Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of lymphoid neoplasms resulting from monoclonal proliferation of malignant lymphoid cells in the blood, bone marrow, and other organs.[1] ALL accounts for 25% of childhood malignancy with an annual incidence rate of 3 to 4 cases per 100 000 children under 15 years of age.[2, 3] Nowadays, owing to intensive chemotherapy methods, the outcomes of ALL have significantly improved and the complete response rate is about 80%.[4] Over the past five decades, the outcome of childhood ALL has evolved from a median survival of two months to a long-term survival rate.[5] Substantially, since 1970, intensified treatment protocols have been introduced via the UK Medical Research Council (MRC) in accordance with the risk stratification of children in all risk groups.[6] UK-ALL X protocol has been made of vincristine, prednisolone, daunorubicin, and asparaginase (6000 IU/m^2 3×week×9) identical to UKALL VIIIB along with intrathecal methotrexate on days 1, 15, and 29.[7] Despite dramatic survival improvement (roughly 5-year overall survival (OS)) following intensive consolidation therapy, relapse is the leading cause of treatment failure in 15-20% of patients.[2,8] Moreover, the survival rate following relapse is still partly low.[9] Furthermore, contemporary implementation of intensification therapy entails mild to severe complications in patients and the frequency of treatment-related mortality is reported to be 2-4%.[10,11] In addition, the most life-threatening complications of prolonged treatment protocol are febrile neutropenia and infection in children with ALL.[11,12]

Therefore, the outcomes in children treated by the MRC UKALL X trial were analysed in order to evaluate the complications of the treatment protocol in childhood ALL in the hope of finding effective strategies to reduce the treatment-related mortality and morbidity.

Materials and Methods

This is a retrospective study conducted at Bahrami University Hospital, Iran on children with ALL between 2008 and 2015. After receiving the ethics approval by Tehran University of Medical Sciences and informed consent, patients' demographic data and clinical characteristics, including age, gender, ALL morphology subtype, WBC, and neutrophil counts, Hb level and outcome-before and after every session of consolidation treatment and also in the interval between occurrences-were collected with the standard available data sheets.

Neutropenia

Criteria for the diagnosis of treatment-related neutropenia were described as the reduction in neutrophil counts appearing from the onset of treatment until 30 days.

Ethical consideration

This research study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all patients. The study was further approved by our Institutional Review Board.

Statistical analysis

Data were analysed using statistical package for the social sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. Data were presented as mean/median values and percentages. Cox-proportional hazard model was employed for multivariate analysis.

Results

A total of 75 children with ALL were examined, 67 of whom were treated by UKALL X trial. The mean age of patients was 6.78 years (1.5 months to 15 years, Mod: 5, SD: 4.148). Table1 shows patient demographic data and clinical characteristics. The preponderance of males was in relapsed and expired groups, implying the common referral pattern in Iran.

Due to the abnormal distribution of patient population, independent non-parametric test was utilized to investigate the relationship between mortality and age. The average age in three-year-survival group and mortality group was 6.92 (SD:

3.96) and 6.35 (SD: 7.47), respectively. (P= 0.38)

Thirty-two patients received consolidation therapy, 35 patients received second-line therapy, and 23 cases completed both stages.

Data on WBC and neutrophil counts and hemoglobin level prior to the onset of treatment were recorded for both consolidation and second-line therapy. These data were further recorded in cases of hospitalization for neutropenia and at the time of discharge.

Neutropenia appeared approximately 12 days (SD: 2.66) and 12.63 days (SD: 4.83) after consolidation and second-line therapy, respectively.

Among 33 patients receiving consolidation therapy, 17 cases (51.5%) showed neutropenia, which also was the case with 19 patients from all 35 subjects who had received second-line therapy. No neutropenia-related mortality was reported following consolidation therapy.

Mean duration of hospitalization subsequent to consolidation in all patients and the neutropenic group was 4.8 (SD: 4.032) and 7.47 days (SD: 2.183), respectively. Concerning second-line therapy, duration of hospitalization was 5.51 (SD: 6.161) and 10.6 days (4.682) in all patients and in neutropenic cases, respectively.

Further evaluation was the association between neutropenia after each phase of consolidation therapy and the age of patients. In the first phase, the mean age was 6.59 (SD: 4.22) and 6.72 years (SD: 3.61) for neutropenic and non-neutropenic patients, respectively (P value= 0.8) (Mann–Whitney U = 129.000).

For the second cycle of consolidation therapy, the mean age of neutropenic and non-neutropenic patients was 6.58 (SD: 4.36) and 6.81 years (SD: 3.31), respectively (Mann–Whitney U = 137.000).

Discussion

This retrospective analysis focused on treatment-related complications in children with ALL receiving the MRC UKALL X protocol. Similar to previous reports, higher incidence in males (~ 65%) and in the age group of 0-5 years was observed in the population study. No obvious differences were seen regarding morphology incidence in contrast to previous studies, hence the possible necessity of a larger sample size.

Neutropenia is one of the significant complications of chemotherapy in ALL patients, making them susceptible to a variety of infections. The duration of treatment-induced neutropenia is assumed to be the most important risk factor for infections in pediatric malignancies. It is also to be noted some studies have suggested that neutropenia is not the only risk factor in the development of infectious complications during chemotherapy.[13] There are few reports on infectious morbidity rates in childhood ALL in Iran.

In a recent study, treatment-induced neutropenia was considered as a neutropenia presenting during the first month of treatment.

In the first three years of the disease, 89.5% of the patients were hospitalized due to neutropenia and fever, with the mean of neutropenia duration being 29.32 days. In another study, a higher incidence of fever, infection, and neutropenia and a higher frequency of antibacterial therapy were found in patients under 2.5 years, compared with the older groups.[14] In 2000, Namic Ozbek et al. compared the effects of three different treatments, namely granulocyte-colony stimulating factor (G-CSF), high dose methylprednisolone (HDMP), and G-CSF combined with HDMP, in neutropenic patients on maintenance therapy for ALL. They concluded that G-CSF may induce an increase in peripheral stem cell numbers, confirming hematopoietic recovery by the increase in IL-3 in patients with chemotherapy-induced neutropenia.[15] In another study, it was concluded that prophylactic G-CSF did not have any effects on children with high-risk ALL.[16] In 2014, Ting-Chi Yeh et al. showed that prophylaxis with ciprofloxacin and voriconazole or micafungin could reduce the rates of bloodstream infection and invasive fungal infection (IFI) in children with acute leukemia undergoing intensive chemotherapy.[17]

According to this investigation, the mortality percentage was 25.4% (17 cases) in the first three years of treatment. Although the findings indicated

Table 1. Patient demographics and clinical characteristics

	No. of patients	Male	Female
All patients	67	44 (65.6%)	23 (34.4S%)
Age			
0-5	28 (41.7%)		
5-10	20 (29.8%)		
10-19	19 (28.3%)		
Relapse characteristics			
Time to relapse>3 years	7 (10.4%)	5 (11.36%)	2 (8.3%)
Mortality	17 (25.4%)	12 (27.2%)	5 (21.7%)
Ages			
0-5	8 (47%)	4 (23.5%)	5 (29.4%)
5-10			
10-15			
ALL subgroups			
L1	45 (67.2%)		
L2	22 (32.8%)	14 (31.8%)	8 (34.7%)
Hospitalization (in the first 3 years of treatment due to neutropenia)	60 (89.5%)		

that the highest mortality rate was observed in 0-5 years of age (47%) and in boys (21.7%), none of them occurred following consolidation therapy. Hargrave and his colleagues analysed data from all patients entered in the MRC UKALL VIII, X and XI trials between 1980-1997 to compare the causes of treatment-related mortality (TRM). Based on their findings, bacterial and fungal infections were the main causes of mortality and from the eight deaths associated with the early intensification block on the fifth week, three patients were under treatment by UKALL X protocol.[18]

In the study of David O'Connor et al., 117 cases of all patients under investigation in the UKALL 2003 trial passed away due to treatment complications. Moreover, sepsis was the most common cause of treatment-related mortality (TRM), particularly during neutropenia period with the most incidence in girls.[19] Moreover, in 2016, 409 children with newly diagnosed ALL were observed and assessed for infection and it was concluded that young age, intensive chemotherapy, and no increase in neutrophil count following dexamethasone treatment were associated with infection-related complications.[11] Based on other studies and the recent findings, it can be said that intensive chemotherapy, especially that containing dexamethasone is able to treat neutropenia, thereby reducing TRM.

In a recent study, relapse occurred in seven patients (10.4%) in the first three years of treatment, showing a relatively favourable response to therapy in the patients. As a matter of fact, there is no assurance to the outcome of the 60 other patients being in remission because some patients may relapse after three years.

The Berlin–Frankfurt–Munster (BFM) group divided the relapse period into three categories: very early (earlier than 18 months from the diagnosis), early (later than 18 months from the diagnosis and earlier than six months from the end of the treatment), and late (later than six months from the end of the treatment), and showed that late relapse was associated with a good prognosis.[20]

It is well-known that almost all patients undergoing remission by the end of induction therapy will relapse without further treatment.[21] Allogeneic hematopoietic stem cell transplant (HSCT) has proved a relatively safe treatment, yet not necessary for all patients as a post-remission therapy.[22]

Ajay Vora et al. showed that event-free survival with augmented post-remission therapy was significantly more acceptable than that with standard therapy owing to the reduced rate of relapse. However, the asparaginase and intravenous methotrexate used in the augmented treatment regimen caused more complications.[23] The challenges of balancing between the efficacy and the toxicity of combination therapy in relapsed cases are yet to be surmounted. Management of relapsed ALL is a medical priority with the aim of further improving the outcome of patients.

Overall, due to the approved fact that late relapse is a desirable prognostic factor, one might be led to speculate the relative success of this protocol in the field of remission, while prior to being generalized, these findings must be evaluated in a larger population.

These findings could also be utilized to include the data of other countries, whether or not the massive and demanding steps of this protocol could be taken with similar results.

Finally, given the three-year survival and non-existence of mortality-related neutropenia after consolidation therapies and the low relapse rate, this therapeutic protocol can be a suitable one for childhood ALL in Iran.

Conflict of Interest

None declared.

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