ARTICLE

Risk Factors for Relapse in Patients with Standard Risk B Cell Acute Lymphoblastic Leukemia in a Tertiary Hospital: A Retrospective Case Control Study

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OBJECTIVES: The overall survival of pediatric acute leukemia improved to >90% in developed countries with chemotherapy but relapse rates still remain at 10% to 20% in developed countries. This study aim to determine the risk factors for relapse in pediatric Standard Risk B Cell ALL. Specifically to describe and compare the socioclinical profile of patients under the relapse and non relapse group.

MATERIALS AND METHODS: Medical records of all children diagnosed with B Cell ALL were reviewed. Demographics and clinical data of patients who relapsed were compared to those who did not. The timing, site and outcome of patients who relapsed were noted. Risk factors for relapse were determined by logistic regression analysis to identify risk prognostic factors of relapse.

RESULTS: A total of 226 patients were included with 58 patients who relapsed and 168 who did not relapse. The mean age of diagnosis in both groups were 4y/o. Majority of the relapsed patients were male 35 (60%) and from outside NCR 35 (60%). Among the risk factors evaluated only the duration of chemotherapy induced agranulocytopenia of > 7 days was identified to be significant risk factor for relapse, p value 0.001.

CONCLUSIONS: The present study determined that > 7 days duration of chemotherapy induced agranulocytopenia is a significant risk for relapse. Future studies with a larger population should be conducted to determine the factors for prolonged chemotherapy induced agranulocytopenia resulting to therapy interruptions that compromises treatment outcome. Cytogenetic and molecular approaches for relapsed ALL would help improve treatment strategies for these patients.

KEYWORDS: *leukemia, bone marrow, relapse, lymphoblast, chemotherapy*

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood which accounts of more than 80% of all pediatric ALL. This can be classified into two main subtypes, B-cell acute lymphoblastic leukemia (B-ALL) and T-cell lymphoblastic leukemia (T-ALL), B-ALL being the most common subtype. Diagnosis of ALL at presentation was based on the results of bone marrow morphology, where the leukemic blasts were counted for more than 25% in the marrow space. With new chemotherapeutic modalities, the overall survival of Pediatric ALL improved up to >90% in developed countries, however relapse rates still remain at 10% to 20% in developed countries. (1)

Diagnostic strategies like bone marrow aspirate, biopsy and peripheral blood count have improved the diagnosis of pediatric ALL. Risk factors including osteonecrosis, adolescence, hyperlipidemia, ionizing radiation, genetic diseases, and Down syndrome can predict the occurrence of ALL. (1) The factors affecting the prognosis in ALL include the patient's age, WBC count, genetic/ cytogenetic/immunophenotypic subgroup, and CNS involvement, which are of great importance in investigating the risk and prognosis of ALL in children. The children's oncology group (COG) and the children's cancer group (CCG) identified a set of risk criteria classified as high and standard risk. (2) Standard-risk patients are aged 1-9.9 years with a WBC count of less than 50,000 at presentation, lack unfavorable cytogenetic features, and show a good response to initial chemotherapy. (2)

Relapse is the most common cause of treatment failure and death. Most relapses occur during treatment or within 2 years after treatment completion, some were reported 10 years after diagnosis. (3,4) Recent studies include age, initial WBC count, immunophenotype, cytogenetical or molecular abnormalities, agranulocytopenia and treatment delays during chemotherapy as risk factors for relapse. (5) Agranulocytosis, also known as agranulosis or granulopenia, is an acute condition involving severe and dangerous neutropenia. Agranulocytosis is a condition in which the absolute neutrophil count (ANC) is less than 100 neutrophils per microlitre of blood. Cancer patients with agranulocytosis are at a very high risk of severe infection (6). Acquiring severe infections can cause significant delay in the treatment of leukemia which may also contribute to the risk of relapse. The most common site of relapse is the bone marrow, isolated (74% of relapses), other sites are testicular or CNS (about 12%), and some had both CNS and testicular relapse. (3,7) The Berlin-Frankfurt-Münster (BFM) stratification classify relapse as very early in those occurring <18 months from diagnosis; early relapses in those patients between 18

months and 30 months from remission and late relapse in those ≥ 30 months from remission. (7) Currently, with the use of intensive chemotherapy and with increase in the support therapies such as blood transfusions and antibiotic therapy, around 70 to 75% of affected children can be cured with present treatment protocols. But despite improvements in chemotherapeutic regimen, the survival rate after relapse is still relatively poor with an overall survival rates ranging from 15 – 50%. (3,8,9)

The study aims to explore and determine risk factors for relapse in a lower middle income country to guide in improving risk stratification and management to improve the survival rate with standard risk B Cell ALL patients.

Materials and Methods

This is a case control retrospective study employing review of charts of all patients diagnosed with B Cell ALL on Standard Risk Protocol between January 2017 to December 2023. The study includes patients diagnosed with B Cell ALL between January 2017 to December 2023 and on Standard Risk Protocol. Patients with Down syndrome, those who died during induction phase, had failure of induction, abandoned treatment, and those who were diagnosed and treated at other institutions were excluded in the study. The patients were divided into the Non Relapse group and the Relapse group.

Using OpenEpi (Sample Size for Unmatched Case-Control Study), the computed sample size was 226, 57 cases and 169 controls for a ratio of 1:3 based on the proportion of controls with exposure at 64% to detect an odds ratio of 0.40 with a level of significance of 5% and a power of 80%. Prevalence of controls with exposure was based on prevalence of non-relapse among males from the study of Cheng (2023) done in Philippine Children's Medical Center.

Demographics (age, sex and geographic region) and clinical data (presence of organomegaly, mean initial WBC count, initial hemoglobin and duration of chemotherapy induced agranulocytopenia) were collected in both groups. In the relapse group the timing of relapse (early or late) and site of relapse (isolated marrow, CNS, testicular, concurrent bone marrow or other extramedullary) were included.

Outcome of relapse group is categorized as alive with disease, alive without disease and died.

The data gathered was encoded and tabulated using MS Excel. Statistical analysis used MS data analysis Took Pak, Jamovi software, and Real Statistics applications. Descriptive and inferential statistics were used in the description and analysis of data.

Frequencies and percentages to describe the socio and clinical profiles of patients diagnosed with B Cell ALL were employed. In determining and comparing the clinical characteristics and clinical outcomes of the patients according to group classification (relapse and not relapse), appropriate non-parametric tests like Chi-square, Fisher's Exact, Gamma and Lambda tests were applied. Basic assumptions were observed in the use of Chi-Square test. Binary logistic regression was applied in determining, identifying and analyzing the data that contribute to the relapse of B Cell ALL patients. A p-value of ≤ 0.05 was considered significant.

RESULTS

Of 396 records reviewed, a total of 226 patients were included in the study with 58 relapsed and 168 were non-relapsed patients, respectively. Table 1 highlights the socio-clinical characteristics of the patients for both groups.

Table 1. *Demographic and clinical factors and association with relapse of standard risk B Cell ALL patients*

SOCIOCLINICO FACTORS	GROUP		ASSOCIA-TION
	RELAPSED	NON-RELAPSED	P value
	N = 58	N = 168	
DEMOGRAPHICS			
Age at diagnosis (mean ±SD)	4.05 ±2.06	4.11 ±2.03	0.844[a]
Sex (n, %)			
Male	35 (60)	105 (63)	0.771[b]
Female	23 (40)	63 (47)	
Geographic Region			
National Capital Region	23 (40)	70 (42)	0.684[b]
Outside of NCR	35 (60)	98 (58)	
CLINICAL			
Organomegaly at presentation, (n, %)			
Yes	20 (34)	83 (49)	**0.049[b]**
No	38 (66)	85 (51)	
Initial WBC Count (mean ±SD)	8.70 ±8.13	10.02 ±11.43	0.404[a]
Baseline Hemoglobin Level (n, %)			
< 80 mg/dl	31 (53)	81 (48)	0.492[b]
> 80 mg/dl	27 (47)	87 (52)	
Duration of chemotherapy-induced agranulo-cytopenia (n, %)			
≤ 7days	6 (10)	41 (24)	**<0.001[b]**
>7 to 21< days	25 (43)	102 (61)	
≥ 21 days	27 (47)	25 (15)	

a Linear regression

b $\chi 2$ test of association

*significant @ ≤ 0.05

The mean age at diagnosis is 4y/o in both groups. Majority were males on both relapse and non-relapse groups, 35 cases (60%) and 105 cases (63%) respectively. There were more cases, 133 (59%), from outside National Capital Region. Most of the cases in both groups have no organomegaly on initial presentation, 38 (66%) and 85 (51%) cases for non-relapse and relapse groups respectively. Organomegaly was seen more in non-relapse patients (49%). The mean initial WBC were 10.02 ±11.43 for non-relapses and 8.70 ±8.13 for relapse group, there was no significant difference between the 2 groups. There were more cases under the relapse group with hemoglobin level <80mg/dl, 31 cases (53%), as compared to 27 cases (47%) with hemoglobin >80mg/dl. Under the non-relapse group, most cases, 87 (52%), were >80 mg/dl.

In terms of the duration of chemotherapy induced agranulocytopenia, there were more cases who had agranulocytopenia ³ 21 days under the relapse group. Six cases (10%) had agranulocytopenia of £7 days, 25 cases (43%) had agranulocytopenia of > 7 to < 21 days, and 27 cases (47%) ≥21 days. As for the non-relapsed group, 41 (24%) had agranulocytopenia of £7 days, 102 (61%) had >7 to <21 days, and 25 (15%) ≥21 days. A p-value of 0.001 indicates that there is a significant difference between the different durations of chemotherapy-induced agranulocytopenia which is a significant risk factor for relapse in patients with B Cell ALL standard risk.

As shown in table 2, of the 58 relapse cases, majority were late relapsers (³ 18 months) with 33 cases (57.9%). The most common site of relapse was isolated bone marrow with 41 cases (70.7%). The relapse rate was noted to be 25.7%.

Table 2. *Clinical data of standard risk B Cell ALL relapse patients*

CLINICAL DATA	***RELAPSE***	
	N = 58	**%**
I. Timing of relapse		
Early relapse	24	42.1
Late relapse	33	57.9
II. Site of Relapse		
Isolated marrow	41	70.7
Isolated CNS	12	20.7
Isolated Testicular	3	5.2
Concurrent marrow	2	3.4
Other extramedullary	0	0

For the outcome of relapsed patients diagnosed between 2017 to 2024, 40 cases (69%) died, 17 (29.3%) were alive with disease and either ongoing chemotherapy or on comfort care and 1 case (1.8%) was alive without disease and currently on surveillance monitoring. The mortality rate was computed to be 69% in relapsed cases.

Binomial logistic regression of risk factors that contribute to the relapse of standard risk B Cell ALL is shown in Table 3. Using multivariate analysis, only the duration of agranulocytopenia was a significant determinant for relapse (OR 0.14, p <0.001), which means that a longer duration of agranulocytopenia is associated with higher risk for relapse.

Table 3. *Logistic Regression of the risk factors that contribute to the relapse of Standard Risk B Cell ALL*

PREDICTORS	***OR***	***p-value***
DEMOGRAPHICS		
Age at diagnosis (mean ±SD)	0.97	0.75
Sex		
Male	Reference	
Female	0.92	0.80
Geographic region		
National Capital region	Reference	
Outside NCR	0.72	0.35
CLINICAL		
Organomegaly		
Yes	Reference	
No	0.52	0.05
Initial WBC Count (mean ±SD)	1.0	0.53
Baseline Hemoglobin Level		
< 80 mg/dl	Reference	0.61
> 80 mg/dl	1.19	
Chemotherapy Induced-agranulocytopenia		
≤ 7days	Reference	
7 days to 21 days	0.61	0.328
≥ 21 days	0.14	<0.001

DISCUSSION

In the Western Pacific, one of the leading causes of death and disability is due to cancer. In the Philippines 4,700 children (aged 0 to 19 years) are diagnosed with cancer each year, majority were leukemia accounting approximately 49% of childhood cancers. (10)

The Philippine Cancer Society–Manila Cancer Registry (PCS–MCR) and the Department of Health–Rizal Cancer Registry (DOH–RCR) from 2001-2005 showed an overall absolute survival of 32.3% for childhood ALL. The reported Overall survival of the Cancer and Hematology Division at PCMC of all patients with ALL between 2017 and 2021 from the study of Dr. Cheng last 2023, was 67%. Based on stratification the OS of SR and HR were 75.8% and 56.5% respectively. There were 82 (28.2%) patients who had relapsed. Most of the early relapse were stratified under HR (67.3%) and majority of late relapse were those who are SR (54.6%). Currently, with the use of intensive chemotherapy and with increase in the support therapies such as blood transfusions and antibiotic therapy, around 70 to 75% of affected children can be cured with present treatment protocols. But despite improvements in chemotherapeutic regimen, the survival rate after relapse is still relatively poor with an overall survival rates ranging from 15 – 50%. (3,8,9)

In our study, the mean age of diagnosis for the relapse group was 4.05 ±2.06, which is not a predictor for relapse in standard risk B Cell ALL patients. It was observed in the study that majority of relapse cases, 35 patients (60%), were of male sex. In one study conducted by Tuong and colleagues (2020), male-to-female ratio of 2.71:1 was reported, incontrast with the present study we observed a 1.5:1 ratio which was slightly lower. This findings can be due to a greater number of sample size included in our study. (16) Some studies showed that in males, a trend toward increased bone marrow and testicular relapse were observed, hence in other cooperative groups the length of therapy was longer in males than females in maintennce phase treatment. (17) The current treatment protocol for standard risk ALL at our institution follows a 14 cyles in males during the maintenance phase as compared to 12 cycles in females.

Majority of the population (60%) in relapsed patients were residing outside NCR. These findings can be due difficulties in the logistics and economic factors during follow up that may result to non compliance with chemotherapy schedules. This needs further studies to identify necessary improvement in therapeutic strategies.

In our cohort of relasped patients 38 cases（66% ）do not have organomegaly at initial presentation, at the same time

organomegaly was seen more in non-relapse patients (49%), further analysis using logistic regression shows that organomegaly at initial presentation is not a predictor of relapse.

The mean initial WBC count was 8.70 ±8.13, in relasped group. More patients in the relapsed group have a baseline hemoglobin level of <80mg/dl as compared to relapse patients with >80mg/dl, 31 cases (53%) vs 27 cases (47%). However, hemoglobin levels at presentation is not a predictor for relapse

Increasing duration of chemotherapy induced agranulocytopenia is associated with increased risk of relapse (OR 0.14, 95% CI 0.05-0.39, and p<0.001). Specifically, at least 7 days delay is associated with 2.66 times higher risk for relapse, and at least 21 days delay, with 5 times higher risk for relapse. Interruptions or delays in chemotherapy caused by complications of prolonged agranulocytopenia can compromise treatment outcomes. The study of Yeoh *et al* (2017) showed that the risk of relapse did not differ between patients with longer or shorter delay during the total length of treatment or during the intensive phase. However, it was observed that the length of delays during maintenance phase is a significant risk factor in developing relapse. (24). In the study of Zhang et al, according to Kaplan-Meier analysis, there were significant differences in relapse rates between patients with time of agranulocytopenia £7 days and those with time >21 days ($p<0.05$), but no significant differences between patients with 7 days < time ≤ 21 days and >21 days ($p>0.05$), or between 7 days ≤ time 21 days and time ≤ 7 days ($p>0.05$).

Survival of relapsed patients can be predicted by site of relapse length of first complete remission and immunophenotype. Bone marrow and early relapse are associated with worse prognosis than isolated extramedullary or late relapse. (26) Some late relapses are thought to arise from a common precursor that retains the chemosensitivity of the original clone, which could explain the high cure rates achieved with chemotherapy alone in late relapses. (27) In this study, majority of Standard risk patients were late relapsers (57.9%) which was similar with the findings of Cheng *et al* (54.6%) and Chu *et al* (54.3%). Twenty four (42.1%) of the relapse cases were early relapsers, this can be due to an existing new biomarkers which are still under investigation. (28)

The most common site of relapse was the bone marrow (70.7%) which was consistent with other international data, 60% to 80%. About 50% of relapsed ALL patients do not respond to salvage therapy or suffer a second relapse. For these patients, prognosis is extremely poor with survival rates below 10%. Despite intensive chemotherapy and supportive treatment most children with relapse die. (26) In our study, 40 cases (69%)

relapse die. (26) In our study, 40 cases (69%) of relapsed patients died, 17 cases (29.3%) were alive with disease and one patient (1.8%) in second remission. Those patients who are alive with disease, 4 cases (24%) are on oral metronomics while the other 13 cases (74%) are currently on intensive chemotherapy, either on MSK protocol or on Isolated CNS protocol. Only 1 (1.8%) patient achieved second remission after intensive chemotherapy and on the second year of surveillance monitoring.

Conclusion

The present study determined that the duration of chemotherapy-induced agranulocytopenia is a significant risk for relapse in patients with standard risk B Cell ALL. The longer the duration of agranulocytopenia, the higher the risk for relapse. Future studies with a larger population should be conducted to determine the factors for prolonged chemotherapy induced agranulocytopenia resulting to therapy interruptions that compromises treatment outcome. It is also important to establish which treatment phase of the chemotherapy protocol significantly had agranulocytopenia so that supportive interventions can be introduced and early anticipation is implemented. Lastly, the cytogenetic and molecular approaches for relapsed ALL would help improve treatment strategies for these patients.

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