Acute lymphoid leukemia in Lebanese children: A retrospective study

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ABSTRACT

Acute lymphoid leukemia (ALL) is the most common malignant disease affecting children, accounting for approximately 25% of all childhood cancers. Hence, the majority of these children are in developing countries. ALL is one of the major public health problems affecting the Lebanese children. Our objective was to investigate the epidemiology, laboratory findings and treatment efficacy in ALL children and extrapolate these results to the guidelines used internationally. This retrospective observational cohort study was performed using routine clinical data of 75 ALL children, with age ranging from 0 to 18 years old, attending three major hospitals in Beirut (Lebanon) over a period of thirteen years. Our results showed that males constituted 54.6% of all ALL patients and that ALL is predominant between ages 3–6 years, and that 85.3% of children were pre B-cell ALL. Furthermore, the results showed that there was an association between ALL type and age. Male patients had the highest numbers of high and low risk patients. Moreover, 48% of ALL patients had a WBC count less than 10,000/ μ L. An association was found between risk group and initial WBC. Cytogenetic abnormalities were detected in 17% of all patients. 73% of the patients cleared their lymphoblasts by day 15 of induction. Moreover, 63% of patients were free of disease for more than 5 years and 27% had complete remission, while 8% of patients died; of whom one had Down syndrome.

This study highlights the situation of ALL in children in Lebanon. It provides a realistic overview that may help establish national guidelines for the investigation and management of childhood ALL.

1. Introduction

Childhood cancer is the major cause of death from disease in the children of developed countries.¹ Acute Leukemia (AL) make up approximately one-third of all childhood malignancies with ALL representing 80% of AL in children.^{2,3} In the US, each year 2000–2500 new cases of childhood ALL are diagnosed.⁴ In Lebanon, on the other hand, the percentage of AL of all childhood malignancies is 29.3% distributed between 64% of ALL, 21.4% of AML and 14.6% of unspecified AL according to the latest Lebanese Ministry Of Health's National Cancer Registry readings, i.e. in 2015.⁵

ALL is more prevalent in males⁶ ALL risk increases with the coexistence of inherited conditions such as Down and Klinefelter syndromes, Ataxia-Telangiectasia, neurofibromatosis, Li-Fraumeni, Fanconi's anemia.^{3,7}

The primary treatment of AL is chemotherapy. However, some individual cases necessitate hematopoietic stem cell transplant.³ The latter, joined together with new targeted therapy, has improved that the 5-year survival rate for children with ALL is more than 90% in the high-income countries.⁸

Despite the existence of a Lebanese National Cancer Registry, there are challenges in accurately reporting the ALL data due to lack of studies specificity, noncompliance of the patients in their follow up especially with the different ethnicities nowadays present in the country, and the diversification of its cancer centers. We analyze, thereby, the prevalence of ALL in children in 3 hospitals in Beirut, Lebanon; as well as its relation to age, sex, and the effectiveness of chemotherapy protocols applied. We also present the immunophenotypic and cytogenetic profiles of those children, all of which is distributed over a thirteen year period.

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2. Materials and methods

2.1. Study design and data collection

This is a retrospective observational cohort study designed over an extent of 13 years. Permission to retrieve patient data was granted from appropriate authorities of 3 major hospitals in Beirut (Lebanon): Rafic Hariri University Hospital, Bahman Hospital and Zahraa University Hospital. The study was approved by the research ethics boards in each hospital and conducted with informed consent by the patients' parents. Investigations were performed in accordance with the Principles of the Helenski declaration (1964) for ethical standards. Seventy five (75) Lebanese children of both genders, aged between 0 and 18 years, newly diagnosed with ALL from 2005 to 2017 were included in this study. They included all the pre-treatment laboratory and imaging workup and treatment admissions. The sheets featured history and physical examination of the patients, therapy used during admissions with corresponding dosages, nursing and medical notes regarding follow up inside the facilities as well as at home. Notes regarding emergency department visits were also registered. The following variables were analyzed: age at diagnosis, sex of the patients, type of ALL, white blood cell count at diagnosis, flow cytometry, molecular studies, response to induction therapy (on day 15), area of origin and risk group. It is essential to declare that the following were not taken into account: specificity of clinical manifestations, laboratory testing other than White Blood Count, leukemia and/or its treatment complications (such as tumour lysis syndrome) and cerebro-spinal fluid contents.

2.2. Patients and methodology

These patients were admitted with signs and symptoms of ALL as following: Hepatomegaly, Splenomegaly, lymphadenopathy, pallor, fever, fatigue, bone pain, bruising/petechia, bleeding, infections, rash, cutaneous nodules, testicular enlargement, disseminated intravascular coagulation, seizures, coma, respiratory distress, end stage organ failure. Patients who had received the initial treatment elsewhere or presented with relapse for the first time were excluded from this study. Patients from nationalities other than Lebanese were also omitted. Laboratory and imaging investigations performed at diagnosis areas following: complete Blood Count with differential, bone Marrow Puncture, C-Reactive Protein, liver screening tests, renal function screening tests, viral infection markers, coagulation indices, bacteriology, blood group, thorax Xray (PosteroAnterior, Lateral), abdominal ultrasound, electrocardiogram and echocardiography and lumbar Puncture (cytology).⁹

Diagnosis was established morphologically on bone marrow smears containing >25% blasts. Smears were performed using May-Grunwald-Giemsa, Periodic acid-Schiff, alpha-Naphthyl Acetate Esterase and Myeloperoxidase colorations. Immunophenotyping by flow cytometry was conducted on bone marrow blood in Ethylene diaminetetraacetic acid (EDTA) tubes by centrifugation using Ficoll-Hypaque. Blasts then were placed in a Becton Dickinson Fluorescence-activated Cell Sorting scan and monoclonal antibodies were diagnostic.⁹ Cytogenetic studies were done on bone marrow blood using conventional karyotyping and Fluorescence in Situ Hybridization in order to define specific translocations, inversions, deletions and other abnormalities within the blasts. DNA was extracted from bone marrow aspirates and subjected to Polymerase Chain Reaction Amplification in order to study molecular biology and specify the culprit gene alterations.

Pediatric ALL patients were classified in risk groups according to ALL Total XV protocol.¹⁰ Response to chemotherapy was evaluated via Minimal residual disease (MRD) by immunofluorescence or molecular biology on day 15 of induction. None of the patients was referred to undergo intracranial radiation.

2.3. Treatment regimens

Patients were classified into one of three categories (low, intermediate, or high-risk) based on the criteria presented in the treatment protocols. Most patients had subcutaneous implantable chamber for the administration of chemotherapy. None of the patients was referred to undergo intracranial radiation.

2.4. ALL TOTAL XV protocol

Patients in the low risk group received the TOTAL XV protocol Low-Risk ALL arm and patients in the intermediate and high risk groups received the TOTAL XV protocol intermediate/high-Risk ALL arm. The mean number of days through which induction was given was 42 days. Treatment consisted of three main phases: Induction (6–7 weeks), Consolidation (8 weeks), and maintenance (120 weeks for females and 146 weeks for males).

Induction therapy: It included prednisone, vincristine, daunorubicin, and asparaginase. Patients with Minimal Residual Disease >1% on day 15 received three additional doses of asparaginase. Subsequent induction therapy consisted of cyclophosphamide (1000 mg/m² intravenous), cytarabine (8 doses each of 75 mg/m² per day intravenous push), and mercaptopurine on days 22–35. Upon hematologic recovery, MRD was assessed and consolidation therapy was started.

Consolidation therapy: It consisted of four doses of high dose methotrexate (2.5 g/m² for low-risk and 5 g/m² for intermediate- and high-risk patients) administered over 24 h each. Mercaptopurine was also given all through consolidation.

Maintenance therapy: During initial maintenance therapy, low-risk patients received daily mercaptopurine and weekly methotrexate with pulses of mercaptopurine, vincristine, and dexamethasone. Two reinduction treatments were given between weeks 7–9 and weeks 17–19. Intermediate- and high-risk patients received weekly asparaginase and daily mercaptopurine with pulses of doxorubicin plus vincristine and dexamethasone. For the remainder of maintenance therapy, low-risk patients received mercaptopurine and methotrexate, with pulses of dexamethasone, vincristine, and mercaptopurine. Intermediate and high risk patients received three rotating drug pairs (mercaptopurine plus methotrexate, cyclophosphamide plus cytarabine, and dexamethasone plus vincristine).

CNS-preventive therapy: intrathecal administration of chemotherapy was given to patients according to their risk group and central nervous system status.

Patients who were still being treated were followed up as they were admitted for treatment, whereas the ones who had finished their chemotherapy have been monitored for 5 years after the end of therapy.

2.5. Statistical analysis

Data was presented by using absolute and percentage frequencies, means, standard deviations, and minimum and maximum values when appropriate. The chi-square test was used for comparing categorical variables. The Man-Whitney test was used for comparing continuous variables. Differences were considered statistically significant at a value of $P < 0.05$. The statistical analyses were performed using Graph Pad Prism 5.

3. Results

AL signs and symptoms of the patients in the study methodology were cited beforehand. The former are not the target of our study. However, it is important to note that there were no neurological manifestations in any of our patients. The median age of males was 6 years at diagnosis (range 9 months–16 years) while the median age of females was 6 years 6 months (range 6 months–17 years). ALL is predominant between ages 3–6 years [Fig. 1]. Males are slightly more predominant

Fig. 1. Distribution of ALL children according age.

than females in ALL. Males constituted 41 (54.6%) and 34 (45.4%) were females [Table 1]. Flow cytometry showed that 64 patients (85.3%) were pre B-cell ALL. 11 (14.7%) children had T-cell ALL with one patient contracting a unique T-cell precursor type of leukemia [Table 1]. No significant association has been found between ALL type and gender ($X^2 = 0.4185$; $P 0.5177$) [Fig. 2A]. There was significant association between ALL type and age ($X^2 = 6.594$; $P 0.0102$) [Fig. 2B].

Median WBC at diagnosis was 10,400/ μ L for males and 10,050/ μ L for females, with a range between 800–129,000/ μ L and 1000–300,000/ μ L in males and females respectively. There was no significant difference between the median of WBC in males and females at diagnosis ($P 0.2848$). 48% of ALL patients had a WBC count less than 10,000/ μ L [Table 1].

ALL patients were classified as such: 36 (48%) as low risk, 17 (22.6%) as intermediate risk and 22 (29.4%) as high risk [Table 1]. There was no association between risk group and gender ($X^2 = 0.5823$; $P 0.7474$) [Fig. 3A]. Male patients had the highest numbers of high and low risk patients whereas numbers did not differ significantly between boys and girls in intermediate risk groups. However, there was significant association between risk level and age ($X^2 = 13.46$; $P 0.0012$) [Fig. 3B]. 57(76%) patients were less than 10 years of age and designated as low risk, having other risk variables considered as well. High risk patients were almost equally distributed between age categories.

There is also a well perceived relationship between risk group and initial WBC ($X^2 = 24.81$; $P 0.0017$) [Fig. 3C]. 24 (32%) patients with initial WBC less than 10,000/ μ L were categorized as low risk, whereas no patients (0%) with WBC above 100,000/ μ L are considered as low risk.

SH analysis using dual color probes was performed for all 75 patients. Cytogenetic abnormalities were detected in 13 (17%) patients,

and normal karyotype was detected in the others. Cytogenetic abnormalities included t(1; 19) in 4 children, t(12; 21) in 7, t(11; 19) in 1, t(4; 11) in 1 and 3 children with Down syndrome which ended up in reduction of the intravenous and Per Os chemotherapeutic doses. One patient had Aneuploidy whereas none had hyperploidy. The majority of children with Cytogenetic abnormalities were females (11 of 13) and 11 children were under 10 years [Table 2].

Most of the patients cleared their lymphoblasts by day 15 of induction, except for 16 (27%) patients. Criteria for response was the presence of a positive Minimal residual disease (>1%).

Concerning the cure rate in our patients: 47 (63%) of patients have been free of disease for more than 5 years and (27%) have complete remission (CR1). One patient had early relapse and received the European relapse protocol COPRALL 2005 (VANDA-BLOC R2-R1-R2) and was transferred for haploidentical Bone Marrow Transplantation (BMT). Her mother had matching HLA by 50%. 6 (8%) patients died, with one of them having Down syndrome. Death aetiologies ranged from hospitalisations for severe infections to infiltration of blasts into the body thereby producing end organ damage.

This study is conducted only on Lebanese children with ALL. There were 4 main areas in Lebanon where our patients originated from: 39% originated from South of Lebanon, 28% came from Bekaa, 26% were located in Beirut and 10% were from Mount Lebanon district.

4. Discussion

This Lebanese retrospective study, carried out in three major hospitals located in the greater Beirut area, shows ALL children coming from all over the country; from 4 out of 8 governorates to be exact. It is noticeable that patients coming from Beirut do not form the largest number with the disease. Conversely, children from the South and Bekaa areas precipitate to our 3 Beirut Centers, probably due to lack of proper hospital facilities in their own governorate of origin as well as want in chemotherapeutic regimen and bone marrow transplant opportunities.

In fact, our patients' ages were consistent with the ALL age distribution observed worldwide.¹¹ In the young adult population, starting 15 years of age, results are less promising with disease-free survival rate of 35%–75%.¹² As the child grows, AML becomes more prevalent. Most common symptoms include the following: hepatomegaly, splenomegaly, pallor, fever, bruising, infections, fatigue, limb pain, hepatosplenomegaly, bruising/petechiae, lymphadenopathy, bleeding tendency, rash.¹³ No CNS manifestations were observed in our patients despite the presence of cerebro-spinal fluid leucocytes in some.

Hyperleucocytosis is observed in 10–15% of patients, as US and European studies show.⁴ This is compatible with our patients' WBC on presentation.

The diagnosis can be made in the presence of an intra/extramedullary infiltrate or via the documentation of an ALL-specific chromosomal derangement. T-cell ALL are more likely to present with extramedullary disease. We had no impediments in our 3 centers' diagnostic tools, for they were available on demand and diagnosis would be provided even the same day of the specimen collection as primordial data.

B-lymphocytic subtypes account for approximately 85% of ALL cases, while T-cell ALL is 15% widespread.^{14,15} Some myeloid markers can be present in ALL. Its clinical and prognostic significance is still unclear. There have been reports of bi-phenotypic acute Leukemia which arises from hemopoietic pluripotent stem cell with the capability of differentiating into both lymphoid and myeloid lineages.¹⁶ Early T-cell precursor and early immature T-ALLs are characterized by a very early differentiation arrest and show unique genetic and transcriptional features that overlap both with T-ALL and AML with a unique biology and poor prognosis.¹⁷ We had one patient with such an immune-phenotype as following: dim CD5, CD7, CD33, CD34, HLA-DR, possible dim CD4 and sCD3 positive in 10%. MRD at day 15 of induction was positive so re-intensification chemotherapy (cytarabine, etoposide, Asparaginase with triple intra-thecal chemotherapy) was given. New

Table 1
Variables of risk stratification of ALL patients.

Variables of risk stratification (N = 75)		Number and percentage
Age	< 10 yrs	57 (76%)
	≥10 years	18 (24%)
Sex	Male	41 (54.6%)
	Female	34 (45.4%)
Acute Leukemia type	B-cell (including precursors)	64 (85.3%)
	T-cell	11 (14.7%)
WBC at presentation	<10,000	36 (48%)
	10,000–24,999	16 (21.3%)
	25,000–49,999	10 (13.3%)
	50,000–100,000	6 (8%)
	>100,000	7 (9.3%)
Bone marrow aspirate on day 15 for ALL and post induction for AML	<5% blasts	67 (89.3%)
	>5% blasts	8 (10.7%)
Risk group	Low	36 (48%)
	Intermediate	17 (22.6%)
	High	22 (29.4%)

Fig. 2. Distribution of ALL children according to ALL type and, (A) gender, (B) age.

Fig. 3. Distribution of ALL children according to risk stratification and, (A) gender, (B) age, (C) the initial WBC.

Table 2

Distribution of cytogenetic abnormalities according to gender and age in ALL children.

Balanced Abnormalities	Female	Male	<10	≥10
t(1; 19)	3	1	3	1
t(11; 19)	1	0	1	0
t(12; 21)	6	1	6	1
t(4; 11)	1	0	1	0
Total	11	2	11	2

ambiguous lineages have been described in literature.⁷

In 2017, a latest study in St Jude's children hospital in Memphis was performed on 488 ALL patients, using the same protocol as we did (Total XV), in order to establish the clinical impact of MRD. Patients with t(12; 21) or hyperploidy >50 had low relapse rate with MRD negative on day 19 of induction chemotherapy (1.9% and 3.8% respectively). On the other hand, high risk B-cell and T-cell ALL had poorer results (12.7% and 15.5% respective risk of relapse) even with negative MRD on day 46 of induction chemotherapy.¹⁸

This illustrates 2 suggestions. The first one is that MRD can become negative independently of the starting risk group. The second suggestion is that the relapse risk takes more into account the risk group rather than the MRD. In fact, risk stratification groups were partitioned by the National Cancer Institute (NCI) as seen in the earlier chemotherapy protocol description. Most of our patients were low risk and had negative

MRD on day 15 of chemotherapy, on some grounds that risk stratification correlated perfectly with those of NCI regarding the prevalence of flatter age and WBC at presentation, irrespective of gender. This is also partly because most of our ALL children had favorable prognostic genetic studies such as t(12; 21) as well as immune-phenotype (B- cell precursor). Habitually, 25% of B-cell ALL cases hold t(12; 21) which leads to ETV6-RUNX1 fusion gene. Hyperploidy is present in 35% of ALL children and is virtually absent if the patients are above 18 years of age with pre-B ALL. The prevalence of t(9; 22), considered very lowly prognosis in pediatric ALL, increases with age, ranging from 2% in patients aged 1–9 years to 8% in adolescents. It is the most common chromosomal abnormality in adults (25%) (12). 80% of infants with ALL have an MLL rearrangement which confers a very dismal prognosis regardless of age and is treated according to a specific chemotherapeutic regimen such as Interfant-06 protocol in infantile age.^{19,20}

Most pediatric ALL regimens are based on the pillars developed by the Berlin-Frankfurt-Münster (BFM) group in the 1970s.¹² In the total XV protocol, the combination of vincristine, L-asparaginase and a glucocorticoid booming induces marrow, CNS and testicular remission in 95% of ALL patients which is the goal of induction therapy.²¹ Consolidation therapy is especially conceived for CNS protection, since it contains bi-weekly intra-theal chemotherapy. In the old days, intracranial radiation used to be executed. However this practice has been abandoned due to numerous complications that ensued. In fact, whole brain radiation with 18–24 Gy may lead to growth hormone deficiency

within 1 year after clonidine stimulation test. The sensitivity of the endocrine system has proven to be excessive in children above that of the adults' and the dreary radiation consequences may last till 20 years after diagnosis. Some Indian oncologists advocate the use of high dose cytarabine instead of whole cranial radiation.¹⁹ As for maintenance therapy, it generally lasts for 2–3 years more in boys than in girls, since it is acknowledged that males relapse more frequently than females. Bone marrow transplant remains the sanctuary in cases where induction fails, patients relapse on treatment or within the first year following conclusion of chemotherapy.³ Translocation t(12; 21), renders leukemic cells susceptible to chemotherapy, hence it increases cure rate.¹² Targeted therapies newly intervene where conventional treatment methods are futile.

Tyrosine Kinase Inhibitors, originally used in ALL children with t(9; 22) translocation with triumph, play a dominant role in successfully inducing remission in AML patients as well.¹² Among these TKI, we point out: simple or combined FLT3-ITD inhibitors, used in malignancies such as Philadelphia Chromosome-positive leukemias, c-KIT, VGFR, PGFR and RAF kinase inhibitors such as results.²²

Our patients who relapsed, did so within 18 months of remission. However, patients who relapse extra-medullary > 18 months of remission or in the bone marrow >36 months from remission, do not benefit necessarily from bone marrow transplant since the outcome is akin chemotherapy usage alone. Targeted immunotherapy plays a leading role in late relapses.¹²

The 5–10 years survival rates in AL in the 1 to 14 year-old population is much higher than the one in teens aged 15 years and above, as per the US Surveillance and End Results (SEER) data.¹² In our study, 63% of the patients have survived beyond 5 years and most of the others are still in remission. If we combine these 2 surviving categories, we perceive that immense improvement has been made in Lebanon in these last few decades in the implementation of treatment according to St Jude Hospital's protocol. Many factors contribute to poor response of some of our patients, besides the risk group¹²:

- Low socioeconomic status and illiteracy of the children's families prevent them from being wholly compliant to the therapies, as many live in rural areas. This has an effect on delays in coming to their appointments and lack in adherence to the correct Per Os medication doses. Some of them are also uninsured or underinsured.
- Low rates of primary care utilization and difference in referral in the areas of origin delays diagnosis. Patients tend to present with more advanced disease and high WBC. Some older patients are led to adult oncologists who use completely different protocols which is why the upper age limit for many Children Oncology Group (COG) trials has been currently raised to age 50. However, this did not occur in our patients.
- Features like age >10 years, WBC count >50,000/mm³, mediastinal lymphadenopathy and CNS leukemia confer the high risk nature to these patients.¹⁵
- Death caused by resistant disease, relapses and infections.

5. Conclusion

We have to emphasize the similarity of the conclusions of our study to other contemporary studies. The Event Free Survival in our study is not comparable to the western data due to the relatively limited but acceptable number of patients included. However, this study provides a realistic overview in 3 centers in Lebanon which can be extrapolated to a national scale only in ALL, provided the rest of the Lebanese centers use the same risk-stratifying chemotherapy regimen as the one used here and amplify the collective cooperation. We are using suitable means to diagnose using cytogenetic evaluation and MRD analysis as well as following the international standards in treatment and offering stem cell transplantation to our Leukemia patients if necessary. We thus recommend to follow the same protocols of treatment used in our study to treat

children with ALL. There remains the issue of patients' family compliance and financial coverage which hinder further improvement. This needs to be seriously addressed, especially with the emergence of newly diagnosed immigrants (which have not been included in this study) in the country. The advent of new biological anomalies and targeted therapies must be incorporated in future studies in Lebanon.

Statement of ethics

The study was approved by the research ethics boards in each hospital and conducted with informed consent by the patients' parents. Investigations were performed in accordance with the Principles of the Helsinki declaration (1964) for ethical standards.

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Author contributions

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Data availability

The data will be available upon request.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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