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CLINICAL CHARACTERISTICS AND TREATMENT RESULTS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN NORTH MACEDONIA

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. This study was designed to determine the clinical, biological features and outcomes among children with ALL treated at the only pediatric hematology-oncology center in North Macedonia.

Patients and methods: Seventy four consecutive children age 1 to 14 years, diagnosed with ALL between January 1, 2010 and October 31, 2017 and treated according to ALL IC BFM 2002 protocol were retrospectively evaluated.

Results: The median age at diagnosis was 5 years and males were predominant (60.8%). Precursor B-cell ALL was diagnosed in 81.1% of patients, while 18.9% had T cell ALL. CNS involvement at the time of diagnoses was present in 6.8% of patients. Complete remission was achieved in 93.2% of patients. The induction death rate was 5.4%. The rate of death during first complete remission was 4.1%. Relapse occurred in 13.5% of patients. After a median observation time of 44 months, the 5-year overall survival (OS) and event-free survival (EFS) rates (± standard error) were 79.4% ± 5.2% and 74% ± 5.7%, respectively. The 5-year EFS rate for patients categorized as standard risk by NCI criteria was significantly higher than for high risk patients (83.3% versus 46.7%; $P<0.001$). Patients with precursor B-cell ALL and negative minimal residual disease (MRD) status at the end of induction had the best prognoses.

Conclusion: Our study demonstrated that the treatment results of childhood ALL in North Macedonia are comparable to those obtained in the ALL IC BFM 2002 trial.

Keywords: acute lymphoblastic leukemia, children, treatment, survival

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer accounting for approximately 30% of all malignancies in children under 15 years of age [1]. Over the last several decades the 5-year overall survival rate for childhood ALL has been dramatically improved reaching up to 90% according to the recently reported data from Western Europe and North America [2-8]. This impressive success in the treatment results can be attributed to a utilization of well–design, standardized treatment protocols through participation of children with ALL in clinical trials that involves

wide national and international collaboration. With multi-agent, risk-adapted chemotherapy regimens improved treatment results have been achieved not only in high-income countries but also in countries with lower income which have reported a 5-year overall survival rate over 80% [9].

Relapses are the main cause of treatment failure in childhood ALL [10]. Several well-defined prognostic factors have been used in determining the risk of relapse and include the clinical features of patients at diagnoses, biologic and genetic features of leukemic blasts and early response to therapy [11-17]. Monitoring of minimal residual disease (MRD) at a specific time points during therapy has been shown to have the highest prognostic value in childhood ALL [2–4, 7, 18–22]. Identification of prognostic variables is important in order to make an accurate risk stratification that leads to reduction of relapses caused by under treatment and toxicities caused by overtreatment.

All children with ALL in North Macedonia aged 0–14 years are diagnosed and treated at the University Clinic for Children's Diseases in Skopje, which is a public health institution financed by the government and a unique Pediatric Hematology/ Oncology center in the country. Each year in North Macedonia, which has about 420 000 children aged 0-14 years [23] are diagnosed approximately 11 pediatric cases of ALL. The treatment of patients over 14 years of age is performed at the Clinic for Hematology. The therapeutic strategy for children and adolescents is based on the most widely used BFM protocols. We here report the clinical and biological features and outcomes of ALL in children treated with ALL IC BFM 2002 protocol adapted to the local settings.

MATERIALS AND METHODS

Patients

From January 1, 2010 to October 31, 2017, 85 patients aged 0–14 years were consecutively diagnosed with ALL in our institution. Of these, 5 patients under 1 year old and 6 patients whose parents refused the treatment in our institution and went to others specialized centers abroad on their own decision were excluded from this analysis. The remaining 74 patients were eligible for this study. Data were retrospectively collected from the hospital electronic system and paper based – medical records. The median follow up period for the analyzed patients was 44 months. The study was approved by the Ethics Committee of the Medical Faculty in Skopje. Written informed consent had been obtained for all patients from their guardians before initiation of chemotherapy in accordance with the Declaration of Helsinki.

Diagnoses

At diagnoses, a complete blood count with peripheral blood smear, bone marrow (BM) aspiration biopsy, routine biochemical analysis, blood group, coagulation tests, microbiological analysis according to clinical indication, serum immunoglobulin levels, serological tests for viral hepatitis, abdominal ultrasound, electrocardiography, echocardiography and chest X ray were performed in all patients. The diagnosis of ALL was established by standard morphological analysis of Giemsa-stained smears of BM if ≥25% lymphoblasts were present and the blast being negative for myeloperoxidase based on cytochemistry. Immunophenotyping was performed by flow cytometry in the laboratory of hematology clinic. Central nervous system (CNS) involvement was diagnosed if more than 5 cells/μL were counted in a non-traumatic cerebrospinal fluid and lymphoblasts were identified unequivocally on cytospin preparations. Molecular diagnostics including the following hybrid transcripts: ETV6-RUNX1, BCR-ABL and MLL-AF4 have been done regularly since 2015 at the Faculty of Pharmacy in Skopje by using a standard reverse transcriptase – polymerase chain reaction (RT-PCR) method. Before 2015, patients were screened only for BCR-ABL in our hospital, but not systematically throughout the entire study period due to limited resources. Cytogenetic examination was performed in a minority of patients, therefore their findings were not evaluated.

Response and Relapse Criteria

Prednisone response was assessed by the absolute blast count in the peripheral blood on day 8, after 7 days of prednisone and one dose of intrathecal methotrexate on day 1. Prednisone good response (PGR) was defined as less than 1 x 10^9/L, whereas prednisone poor response (PPR) was defined as ≥1 x 10^9/L blasts. BM response to induction therapy was evaluated by morphology on days 15 and 33. BM status was categorized as M1 (<5% blasts), M2 (5 to < 25% blasts) and M3 (≥25% blasts). Complete remission (CR) on day 33 was defined as M1 marrow with regenerating haematopoieses and no extramedullary disease. Assessment of MRD status by multiparmetric 6-color flow cytometry in BM

specimens collected on day 33 was performed in the reference laboratory of the General Hospital George Papanikolaou in Thessaloniki, Republic of Greece, as previously described [24]. MRD was considered present if the disease burden was ≥0.01%. Relapse was defined as recurrence of 25% or more lymphoblasts in BM or reappearance of localized leukemic infiltrates at any site. Relapses were classified as very early (within 18 months from the initial diagnoses), as early (after 18 months from the initial diagnoses and up to 6 months after cessation of front-line treatment), or as late (later than 6 months after cessation of front-line therapy).

Treatment

Patients were treated according to the intermediate risk arm of ALL – IC BFM 2002 protocol consisted of induction (protocol I), consolidation (protocol M), delayed intensification (protocol II) and maintenance therapy with a total duration of 2 years [9]. All patients received high dose (5gr/m2) methotrexate in consolidation.

Six children with high positive levels of MRD at the end of induction therapy (≥1%) and 2 patients with BCR-ABL positive ALL were considered to have high risk (HR) leukemia. Consolidation therapy for HR patients was consisted of three intensive multi-agent chemotherapy blocks. Delayed intensification included three high risk (HR) blocks (six HR blocks were applied in total) plus single protocol II or protocol II was given twice based on the physician's decision. Regarding the cases with BCR-ABL positive ALL, imatinib was added to an intensive chemotherapy regimen only in one patient.

Table 1. *Patients Characteristics*

Characteristics	N (%)	Precursor B-cell ALL	T-cell ALL	P-value
Total	74 (100)	60 (81.1)	14 (18.9)	
Sex				0.545
Male	45 (60.8)	35 (58.3)	10 (71.4)	
Female	29 (39.2)	25 (41.7)	4 (28.6)	
Age (years)				0.001
1 to <6	47 (63.5)	44 (73.3)	3 (21.4)	
6 to <10	16 (21.6)	10 (16.7)	6 (42.9)	
10 to ≤14	11(14.9)	6 (10.0)	5 (35.7)	
Initial WBC				<0.001
<50 x10^9/L	58 (78.4)	53 (88.3)	5 (35.7)	
≥50 x 10^9/L	16 (21.6)	7 (11.7)	9 (64.3)	
NCI risk group				0.001
Standard	51 (68.9)	48 (80.0)	3 (21.4)	
High	23 (31.1)	12 (20.0)	11 (78.6)	
CNS involvement				0.004
Present	5 (6.8)	1 (1.7)	4 (28.6)	
Absent	69 (93.2)	59 (98.3)	10 (71.4)	
Mediastinal mass				<0.001
Present	10 (13.5)	2 (3.3)	8 (57.1)	
Absent	64 (86.5)	58 (96.7)	6 (42.9)	
Hepatosplenomegaly				0.165
Present	56 (75.7)	43 (71.7)	13 (92.9)	
Absent	18 (24.3)	17 (28.3)	1 (7.1)	
Lymphadenopathy				<0.001
Present	20 (27.0)	8 (13.3)	12 (85.7)	
Absent	54 (73.0)	52 (86.7)	2 (14.3)	
Baseline laboratory characteristics				
WBC x 10^9/L (mean values ± SE)	47.05 ± 13.54	25.63 ± 4.70	138.88 ± 64.93	0.014
Hemoglobin g/L (mean values ± SE)	81.03 ± 2.68	77.92 ± 2.74	94.36 ± 7.08	0.029
RBC x 10^{12}/L (mean values ± SE)	3.10 ±0.11	2.98 ± 0.11	3.63 ± 0.30	0.027
Platelets x10^9/L (mean values ± SE)	72.24 ± 8.81	75.75 ± 10.60	57.21 ± 9.91	0.710

Abbreviations: WBC-white blood cells, NCI – National Cancer Institute, NCI standard risk group= age 1 to <10 years, and WBC <50x10^9/L; NCI high risk group= age ≥ 10 years or WBC >50x10^9/L; CNS-Central nervous system, RBC-red blood cells; SE-standard error.

Prophylactic cranial radiotherapy (12 Gy) was given in HR patients and T cell ALL. Patients with initial CNS involvement received additional intrathecal doses of methotrexate and therapeutic cranial radiotherapy. Trimethoprim sulfamethoxazole was given in 3 consecutive days per week throughout the whole treatment period and prophylactic fluconazole (5mg/kg/day) during the neutropenic period. In all patients was implanted central venous catheter by experienced anesthesiologist in an operating room.

Statistical Analysis

Clinical characteristics were summarized with descriptive statistics. Groups were compared using the Chi-square or Fisher exact test for categorical variables and the Mann–Whitney U test for continuous variables. Overall survival (OS) was defined as the time from the beginning of treatment to the date of last follow-up or death from any cause. Event - free survival (EFS) was defined as the time from the beginning of treatment until the first event or until the date of last follow up if no event occurred. Events were resistance to therapy and relapse or death from any cause. OS and EFS were estimated using Kaplan-Meier method and groups were compared by log-rank test. Multivariate analysis (Cox proportional hazard regression model) was used to identify independent predictors of EFS. Statistical analysis was done using SPSS (Statistical Package for the Social Science) software, version 23.0. $P < 0.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

The presenting clinical and laboratory characteristics of the 74 patients are summarized in Table 1. The median age at diagnosis was 5 years (range 1-14). Males (60.8%) were predominant in the sample (male/female ratio=1.5). Precursor B cell ALL was diagnosed in 60 (81.1%) children and T-cell ALL in 14 (18.9%). Patients with T-cell ALL, as indicated in Table 1 were more likely than patients with precursor B-cell ALL to be at older age (P=0.001), to have a higher initial white blood cell (WBC) count (P<0.001), to be assign in the high risk group by NCI criteria (P=0.001) and to present more often CNS leukemia (P=0.004), mediastinal mass (P<0.001) and peripheral lymphadenopathy (P<0.001). Also, patients with T-cell ALL were more likely than patients with precursor B-cell ALL to have a higher hemoglobin level at diagnoses (P=0.029).

In our series for BCR-ABL fusion transcript were screened 52 children and two (3.8%) of them were positive. They were treated according to treatment strategy for high risk ALL and both are still alive and without disease. MLL-AF4 was investigated in a small number of patients (n=21) and none of them had a detectible translocation. ETV6-RUNX1 expression was documented in 2 (8%), out of 25 investigated patients.

Table 2. *Chemotherapy response and outcome*

	N (%)	Events (n)	5-year EFS (SE)
Prednisone response	73 (98.6)		
PGR	65 (89)	13	0.770 (0.060)
PPR	8 (11)	4	0.516 (0.178)
BM status, day15	71 (96)		
M1	51 (71.9)	7	0.822 (0.062)
M2	15 (21.1)	5	0.711 (0.123)
M3	5 (7.0)	3	0.400 (0.219)
MRD status, day 33	64 (86.5)		
MRD <0.01%	37 (57.8)	2	0.944 (0.039)
MRD 0.01% - ≤0.1%	12 (18.8)	4	0.750 (0.125)
MRD >0.1%	15 (23.4)	4	0.711 (0.124)

Abbreviations: PGR-prednisone good response, PPR-prednisone poor response, BM-bone marrow, MRD-minimal residual disease, SE-standard error

Treatment results

Response to Induction Therapy

Chemotherapy responses (on days 8, 15 and 33) are outlined in Table 2. Of the 74 evaluable patients, 69 (93.2%) patients achieved complete remission and 5 (6.8%) had induction failure. Four (5.4%) patients died during induction therapy. Their age was between 1 to 6 years and three of them had high initial WBC count (>100 x 10^9/L). In detail, one patient who presented with extreme hyperleukocytosis (WBC 952.5 x 10^9/L) died during prednisone monotherapy as a result of leukostasis complications including intracranial and pulmonary hemorrhage. The second noninfectious cause of death was fatal acute encephalopathy. The other two patients died from infectious causes (severe pneumonia and sepsis), 1 of them had pre-existing chronic cardiomyopathy. These deaths occurred between 2 and 3 week of induction chemotherapy. One patient who presented more adverse risk factors, such as those of older age, high WBC count and T-cell ALL had resistant leukemia and died after 9 months due to disease progression.

Table 3. *Treatment results of 74 pediatric patients with ALL*

	N (%)
Overall	74 (100)
Death before CR	4 (5.4)
Resistant disease	1 (1.4)
CR	69 (93.2)
Death in first CR	3 (4.1)
Relapses	10 (13.5)
Isolated BM	9 (12.2)
Combined BM/CNS	1 (1.4)
Secondary neoplasms	0 (0.0)
Alive in CCR	56 (75.7)
Lost to follow up in CR	4 (5.4)
Total events	18 (24.3)

Abbreviations: CR-complete remission, BM-bone marrow, CNS-central nervous system, CCR-continuous complete remission.

Death in first complete remission, Relapses and Outcome

In our study 3 (4.1%) patients died in first complete remission (according to treatment phase, one patient died during phase IB, one patient during Protocol II and one patient who had Down syndrome died during maintenance therapy). These deaths were related to chemotherapy-associated hematological and non-hematological toxicity. The patient with Down syndrome died from cardiotoxicity and infection. No patients died during the consolidation phase - courses of high dose methotrexate or HR - block therapy.

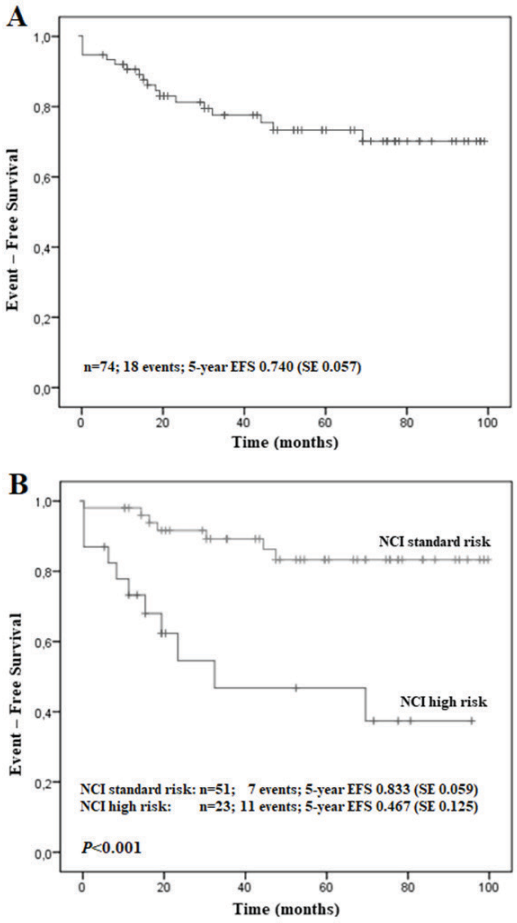

Figure 1. *Kaplan-Meier estimate of event-free survival for evaluable patients (A) and according to NCI risk groups (B).*

Relapses occurred in 10 (13.5%) patients. The most common site of relapse was bone marrow. Only one child experienced combined BM/CNS relapse. Three (30%) relapses were very early, four (40%) early and three (30%) were late relapses, according to BFM criteria. The patients with T-cell ALL had a greater relapse rate than those with precursor B cell ALL (21.4% versus 11.7% respectively). The relapsed patients were treated with conventional poly-chemotherapy with BFM relapse protocols and three of them underwent allogeneic hematopoietic stem cell transplantation in a foreign specialized center, because this procedure for children is still not available in our country. In our series, unfortunately the relapses resulted in high mortality rate (70%) and the most of the children died at the early stages of the re-induction

therapy due to sepsis during the period of aplasia or disease progression.

In this cohort second malignancy was not observed. Follow-up data in continuous complete remission were unavailable for 4 children, because their families have migrated abroad. The treatment results are shown in Table 3. After a median observation time of 44 months (range 0.23-100), the 5 year OS (± standard error (SE)) and EFS (± SE) rates (Fig. 1A) for the entire cohort were 79.4% ± 5.2% and 74% ± 5.7%, respectively. Most of the patients in this cohort were treated according to the intermediate risk arm and their 5-year OS ± SE and EFS ± SE rates were 82,2% ± 5,5% and 75,7% ± 6,2%, respectively

Outcomes by Clinical Features

The 5-year EFS rate for males was 60.8% ± 8.6% versus 89.1% ± 5.9% for females (P=0.059). The 5-year EFS rate for patients age 1 to less than 6 years was 79.0% ±6.3% and for patients age 6 to less than 10 years was 77.8% ± 13.9%. Patients 10 years and older had significantly lower EFS rate (43.6% ± 15.5%) (1<6 years versus ≥10 years P=0.006; 6 to <10 years versus ≥10 years P=0.013). Patients who had an initial WBC count of <50 x10^9/L achieved significantly better 5-year EFS rates compared to children with higher WBC count. The 5-year EFS rates for patients with an initial WBC count <20 x10^9/L and >20-50 x 10^9/L were similar (81.7% ± 6.4% and 80.8% ± 12.2%, respectively) as compared to 32.9% ± 16.4% for those with an initial WBC count >50 x 10^9/L (P<0.001 and P=0.018, respectively). Patients classified as NCI standard risk group had a 5 year EFS rate of 83.3% ± 5.9% versus 46.7% ± 12.5% for those classified as high risk (P<0.001, Fig. 1B). The 5 year EFS rate for patients with precursor B cell ALL was 77.0% ± 6.0%. Patients with T-cell ALL had lower EFS (51.6% ± 17.8%), but the difference did not reach statistical significance (P=0.06, Fig. 2A). CNS involvement at the time of diagnoses was present in 6.8% of patients. They achieved significantly lower 5-year EFS rate of 26.7% ± 22.6% versus 76.0% ± 5.7% for those without CNS disease (P < 0.001).

Outcomes by Early Treatment Responses

The 5-year EFS rate was 77.1% ± 6.0% for patients who had PGR versus 50.0% ± 17.7% for patients who had PPR (P=0.024, Table 2, Fig. 2B). The 5-year EFS rates by BM morphology on day 15 were 82.2% ± 6.2%, 71.1% ± 12.3% and 40.0% ± 21.9% for the patients with M1, M2 and M3 status, respectively (M1 versus M3 P=0.001, Fig. 3A). Patients in the MRD on day 33 groups had a 5-year EFS rate of 94.4% ± 3.9%, 75.0% ± 12.5% and 71.1% ± 12.4% for the MRD <0.01%, 0.01% - ≤0.1% and >0.1% groups respectively (<0.01% versus MRD 0.01% - ≤0.1% P=0.015; <0.01% versus MRD >0.1% P=0.046). By post-induction therapy intensification, of the six patients with MRD levels ≥1%, 5 have remained in remission without relapse.

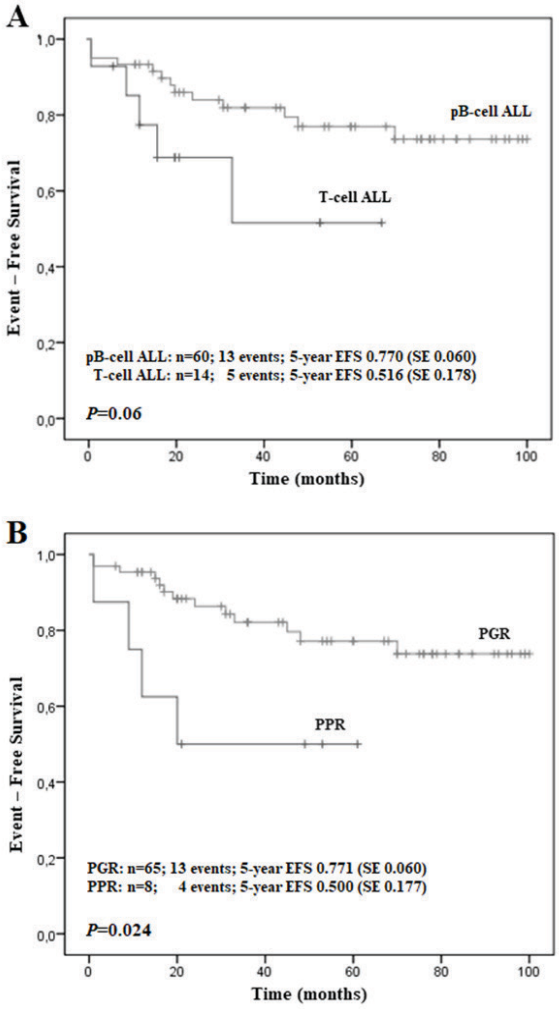

Figure 2. *Kaplan-Meier estimate of event-free survival according to immunophenotype; pB-cell ALL indicates precursor B-cell ALL (A) and according to prednisone response (B).*

Patients with precursor B cell ALL and negative MRD status on day 33 had a 5-year EFS rate of 100% versus 69.8% ± 10.4% for those who had positive MRD status on day 33 (P=0.001, Fig. 3B). Among 12 T-cell ALL patients who were investigated for MRD status on day 33 there were 3 events. Two out of 3 events which were relapses occurred in patients who achieved negative MRD status on day 33.

Multivariate analysis with Cox proportional hazard regression was used to determine the impact of age, presenting WBC count, prednisone response and MRD status at the end of induction therapy on event-free survival. Age was analyzed as a continuous variable, and WBC, prednisone response as well as MRD status as categorical variables. Only prednisone response lost its prognostic significance, whereas the older age (hazard ratio 1.19; 95% CI 1.01-1.41; P=0.036), presenting WBC count ≥50 x10^9/L (hazard ratio 11.78; 95% CI 2.04-67.97; P=0.006) and positive MRD status (hazard ratio 5.69; 95% CI 1.04-31.06; P=0.045) were independently associated with poor survival.

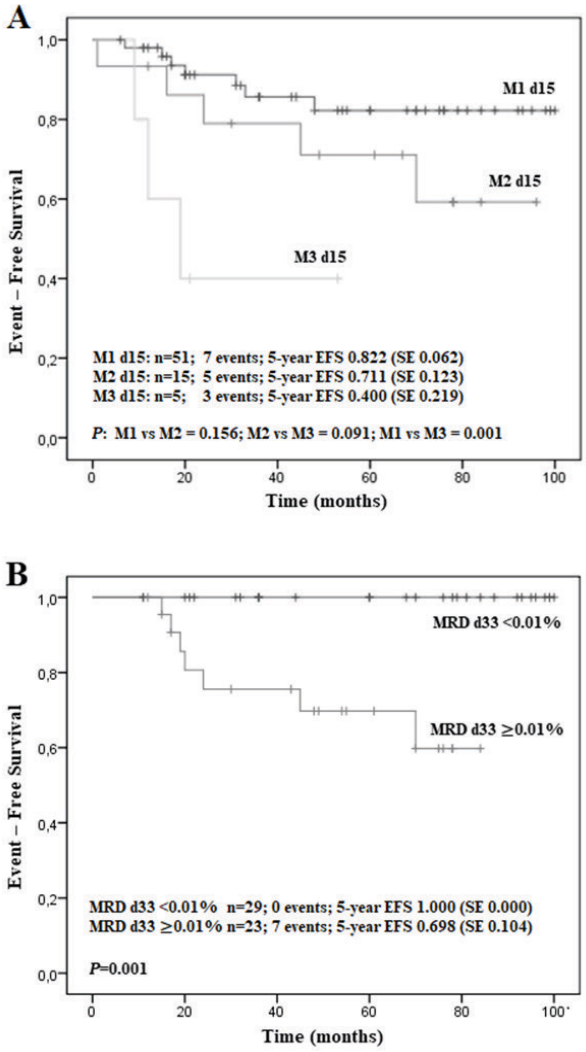

Figure 3. *Kaplan-Meier estimate of event-free survival according to bone marrow response on day 15 (A) and according to minimal residual disease status on day 33 in patients with precursor B-cell ALL (B).*

DISCUSSION

This study presents our experience of treating children with ALL at the only pediatric hematology-oncology center in North Macedonia according to ALL IC BFM 2002 protocol adapted to the local conditions over a period of 8 years.

The presenting features at diagnoses including age and gender distribution and proportion of patients with WBC count >50 000/μL did not differ from those reported in the ALL IC BFM 2002 and other studies worldwide [9, 11, 17, 25]. The incidence of T-cell ALL in this study was 18.9% which appears to be higher than that reported in the ALL IC BFM 2002 (12.7%) and ALL-BFM 95 study (13.3%) [9, 11]. Considering the different ethnic backgrounds of children in North Macedonia, this finding could be related to greater susceptibility to T-cell ALL in certain ethnic groups. It has been established that the ethnic disparities and contributing genetic variables influence on the incidence of the phenotypic subtypes in ALL [26]. The frequency of CNS involvement in our cohort was 6.8% compared with 3.6% in the ALL IC BFM 2002. However, this finding was expected with the higher proportion of patients with T- cell ALL. The differences in clinical features at presentation between patients with T cell ALL and precursor B – cell ALL are well recognized [27]. In our series patients with T-cell ALL were more likely to be at older age and to have a higher presenting WBC count and these unfavorable features together with a higher frequency of CNS involvement might have contributed to the poorer outcome compared with that of patients with precursor B cell ALL.

Investigation of the most common genetic lesions (ETV6-RUNX1, E2A-PBX1, BCR-ABL and MLL rearrangements) which determine the prognoses of precursor B cell ALL was not possible in all patients because of the limited technical conditions in our hospital in the early study period. Therefore, further studies are needed to assess the incidence of genetic subtypes and their prognostic impact among pediatric patients with ALL in North Macedonia.

The high incidence of induction death was an important contributor to decreased survival rate in our study. Association of hyperleukocytosis with a higher risk of death during induction has been shown before by other researchers [28] and was also evident in our study. The 5.4% rate of induction death for our patients was substantially higher compared to results of ALL IC BFM 2002 with induction mortality rate of 2.2% [9]. In the ALL BFM 95 study the rate of death prior to complete remission was 0.7% [11]. The rate of death in first complete remission was 4.1% and this result can compare favorably to that observed in the ALL IC - BFM 2002 (5%), but is still far from what is reported in the major international ALL study groups (1-3%) [2, 11, 29]. Therefore, greater efforts are needed to decrease the treatment-related mortality; in particular, we need better define the subset of patients who are at high risk for treatment-related toxicity, as well as to provide enhanced supportive and intensive care.

Relapsed ALL was the major cause of treatment failure in this study. The relapse rate was greater in T-cell ALL suggesting that this lineage is more drug resistant than precursor B cell ALL [27]. The relapse rate of 13.5% was comparable to that observed in the ALL IC - BFM 2002 and ALL BFM 95 trial (16%) [9, 11]. Despite these encouraging results, the treatment outcome of relapsed ALL in our country is still very poor. Improving the treatment results of relapsed patients remains a significant challenge and novel treatment modalities need to be considered.

The 5-year EFS and OS rates were 74% and 79.4% respectively, which were very similar to those obtained in the ALL IC - BFM 2002 trial (5-year EFS 74%, OS 82%) conducted in 15 upper-middle and high-income countries on three continents [11]. The adoption of this protocol in some low-middle income countries resulted in 20% lower survival rates [30]. The ALL BFM 95 trial, which was the basis for ALL IC BFM 2002 therapy have reported 6-year EFS of 79.6% [11]. The results from AIEOP-ALL 95 study which also utilized BFM chemotherapy have showed 5-year EFS of 75.9% [31].

Presenting features that had significant impact on 5 year EFS were age, WBC count, NCI risk groups and CNS status and these findings were consistent with results reported in the ALL-BFM 95 [32]. Patients with PPR and a slow blast clearance from bone marrow on day 15 defined as M3 status had the significantly shorter EFS, as demonstrated in several other studies [32-34]. MRD measurement at different time points during the first months of treatment has been shown to have the most important prognostic and therapeutic implications [2-4, 7, 21, 22]. In this study MRD levels ≥1% at the end of induction therapy documented in 6 patients were used for additional intensification. Five of those 6 patients have remained in remission without relapse. As the price of MRD analysis has not been covered by Macedonian health insurance fund, a strategy of MRD monitoring at two time points which is a more powerful for predicting treatment outcome [17, 18] could not be done for all patients. In this small study, MRD status at the end of induction therapy was associated with differences in survival, which is in keeping with well-established findings [18-20]. Patients with precursor B cell ALL and absence of the MRD on day 33 had the most favorable outcome. It is important to note that these results were achieved with the intermediate risk arm of the treatment protocol. The multivariate analysis indicated that MRD status at the end of induction therapy was an independent prognostic factor, but this finding remains to be confirmed in a prospective study of a larger patient cohort.

In conclusion, the overall results from this study suggest that adoption of treatment protocols from international randomized multi-center studies can be successfully applied in our treatment center. Eighty percent of children with ALL in Macedonia could be cured with the ALL IC BFM 2002 protocol. However, further diagnostic and therapeutic improvement is needed and that should be addressed to more precisely stratification and improved risk-directed therapy that allows treatment reduction for patients who have the most favorable prognosis and treatment intensification for high risk groups. Greater efforts should be made to improve cytogenetic methodology and to introduce MRD measurement by flow cytometry in our laboratory considering its prognostic and therapeutic implications in the contemporary protocols. Participation in international studies should be encouraged because this is the best possible option for all: the patients, their families and scientific community.

Conflict of interest

The authors declare that there is no conflict of interest

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Резиме

КЛИНИЧКИ КАРАКТЕРИСТИКИ И РЕЗУЛТАТИ ОД ТРЕТМАН НА ДЕТСКАТА АКУТНА ЛИМФОБЛАСТИЧНА ЛЕУКЕМИЈА ВО СЕВЕРНА МАКЕДОНИЈА

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Вовед: Акутната лимфобластна леукемија (АЛЛ) е најчеста малигна болест во детството. Оваа студија беше дизајнирана за утврдување на клиничките и биолошките карактеристики и тераписките резултати кај децата со АЛЛ, кои се лекуваат во единствениот педијатриски хемато-онколошки центар во Македонија.

Пациенти и методи: Седумдесет и четири деца на возраст од 1 до 14 години со АЛЛ, дијагностицирани помеѓу 1 јануари 2010 и 31 октомври 2017 година и лекувани според протоколот ALL IC BFM 2002 беа ретроспективно евалуирани.

Резултати: Средната возраст при дијагнозата изнесуваше 5 години; децата од машки пол беа предминантни (60,8%). Прекурсорна Б-клеточна АЛЛ беше дијагностицирана кај 81,1% од пациентите, додека 18,9% имаа Т-клеточна АЛЛ. Инфилтрација на ЦНС при дијагнозата беше присутна кај 6,8% од пациентите. Комплетна ремисија оствари 93,2% од пациентите. Стапката на индукциска смртност изнесуваше 5,4%. Стапката на смртност во прва комплетна ремисија беше 4,1%. Релапси се јавија кај 13,5% од пациентите. По среден период на следење од 44 месеци, стапката на 5-годишно вкупно преживување и преживување без настан ± стандардна грешка изнесуваше 79,4% ± 5,2% и 74% ± 5,7%, респективно. Стапката на 5-годишно вкупно преживување без настан за пациентите, кои беа категоризирани како група со стандарден ризик според критериумите на NCI, беше сигнификантно повисока во споредба со таа кај пацинтите со NCI висок ризик (83,3% versus 46,7%; $P < 0,001$). Пациентите со прекурсорна Б-клеточна АЛЛ и негативна минимална резидуална болест на крајот на индукциска терапија имаа најдобра прогноза**.**

Заклучок: Нашата студија покажа дека тераписките резултати од децата со АЛЛ во Македонија се компарабилни со тие остварени во клиничката студија ALL IC BFM 2002.

Клучни зборови: акутна лимфобластна леукемија, деца, преживување