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Lymphoblastic lymphomas in children – A single-center experience from Serbia

Jelena Lazić[1,2], Dragana Janić[1,2], Nada Krstovski[1,2], Predrag Rodić[1,2], Goran Milošević[2], Srdja Janković[2], Dimitrije Brašanac[1,3], Lidija Dokmanović[1,2]

[1]University of Belgrade, School of Medicine, Belgrade, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]University of Belgrade, School of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY

Introduction Intensive treatment protocols used for non-Hodgkin lymphoma in children lead to event-free survival rates ranging from 80% to 90%. However, the results are less successful in developing countries. Lymphoblastic lymphoma (LBL) is the second most frequent type of lymphoma in children, contributing with about one third to all non-Hodgkin lymphoma in childhood.

Objective The aim of the study was to evaluate the results of LBL treatment in University Children's Hospital (UCH), Belgrade.

Methods A retrospective analysis of patient records at UCH from 1997 to 2015 was carried out in patients aged 0–18 years, in whom the diagnosis of LBL had been established. Twenty-two children were included in the analysis.

Results Mean age at diagnosis was 10 years, with preponderance of male patients. All patients were treated according to Berlin-Frankfurt-Münster-based chemotherapy protocols. With median follow-up of 91.5 months, five-year probability of event-free survival was 79.5% for all patients, while overall survival was 81.8%.

Conclusion Our results, although slightly inferior to those of leading international groups, reflect a good treatment outcome in our patients.

Keywords: pediatric; lymphoblastic lymphoma; Serbia; children

INTRODUCTION

About 7% of all cancers in children are non-Hodgkin lymphomas (NHL). Lymphoblastic lymphoma (LBL) is the second most frequent type after mature B-cell lymphoma, contributing with about one third to all childhood NHL. LBL comprises a group of tumors of immature lymphoid cells that share the same morphology and immunophenotype with the lymphoblasts of precursor-cell acute lymphoblastic leukemia (ALL). Distinction between LBL and ALL is based on the extent of bone marrow infiltration by lymphoblasts, i.e. infiltration with 25% or more defines ALL, while less than 25% may be seen in LBL [1]. Great majority of pediatric LBL are T-cell LBL [2]. The initial presentation of T-LBL is an anterior mediastinal mass often leading to superior mediastinal syndrome, as well as tumor lysis syndrome [2]. Using modern chemotherapy protocols similar to those for ALL, T-LBL became a highly curable disease, with cure rates as high as 80% [3–6]. Incomplete regression of the mediastinal tumor can be seen in patients with LBL. However, absence or presence of residual tumor after induction chemotherapy could not predict the subsequent course of the disease. For that reason, most authors prefer not to change the treatment in case of partial tumor volume reduction [7]. On the other hand, patients with no response to first-line treatment have a very poor prognosis [8]. Literature reports on LBL in children in Serbia are scarce [9].

OBJECTIVE

Our study presents initial and follow-up clinical data, as well as treatment results of pediatric patients with LBL, treated in a single pediatric center in Serbia.

METHODS

We performed a review of medical records of newly diagnosed pediatric patients with LBL at the Hematology/Oncology Department of University Children's Hospital, Belgrade, from January 1st, 1997 until June 1st, 2015. A diagnosis of LBL was made in 22 children among the total of 93 patients with non-Hodgkin lymphoma. Histopathological analysis was performed by one of the authors (DB). Diagnosis of LBL in most (9/10) patients presenting with pleural effusion was established by flow cytometric analysis of cells in effusion fluid. Disease staging was performed according to the St. Jude classification. We also analyzed the initial complications of the disease. Superior mediastinal syndrome – signs and symptoms caused by compression or obstruction of superior vena cava and/or tracheobronchial compression was noted. Tumor lysis syndrome (TLS) was defined as laboratory and/or clinical TLS as per Cairo–Bishop criteria [10]. The patients were treated according to NHL-BFM-90 and EURO-LB-02 protocols [11, 12, 13]. Clinical and radiological reassessment

Correspondence to:
Lidija DOKMANOVIĆ
Department of Hematology and Oncology
University Children's Hospital
Tiršova 10, 11000 Belgrade
Serbia
lidija.dokmanovic@udk.bg.ac.rs

of the patients was performed on day 15 and day 33 in order to evaluate treatment response, as well as after induction treatment in patients who failed to achieve complete remission (CR) on day 33. Complete remission was defined as complete resolution of tumor mass confirmed by imaging studies (X-ray and/or computed tomography). Written informed consent for the treatment was obtained from patients' parents or guardians. Probability of event-free survival (pEFS) was calculated using the Kaplan–Meier method. The differences in pEFS were compared by Mantel–Cox log-rank test. The pEFS was calculated from the date of diagnosis until the first event (death of any cause, disease progression, relapse or secondary malignancy) or until the date of last follow-up. Time was censored at last follow-up date if no failure occurred or if patient was lost to follow-up after completing therapy. Follow-up was updated to June 1st, 2015. Overall survival was calculated as the percentage of patients who were still alive at the aforementioned date of the last follow-up. Statistical calculations were performed using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA) operating system.

RESULTS

Among 22 children, male to female ratio was 2.6:1, and mean age at diagnosis was 10 years (range 3.5–17.9, median 8.7 years).

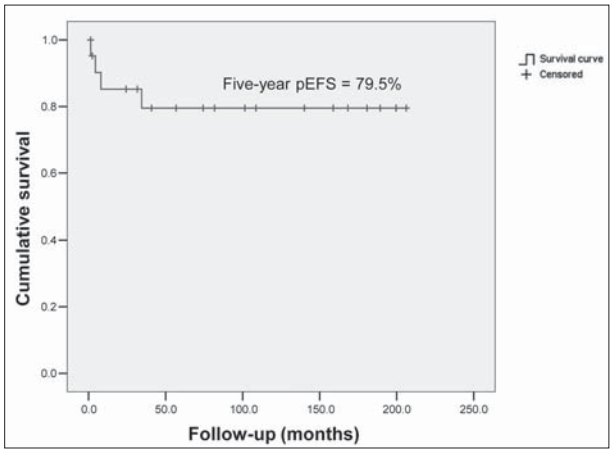
Presenting symptoms, stage, primary localization of the disease, significant initial complications and treatment results are shown in Table 1. Half of the patients presented with breathing difficulties, while palpable tumor masses and cough were seen in more than one third. Duration of symptoms before presentation was two to 60 days (median 30 days) and about 80% of patients had two or more presenting symptoms on admission. Hepatomegaly was detected in five and splenomegaly in three patients. Most patients were diagnosed with advanced stage disease, stage III in 14 (63.6%) and stage IV in seven patients (31.8%). Only one patient had localized, stage II disease, in the neck region. Sixteen patients had mediastinal tumor only, while three patients had mediastinal tumor mass associated with other affected sites: one patient had left tonsillar affection, another patient had a tumor in the right tonsil, while one patient had infiltration of testicles, kidneys and intestines. Three patients presented with extra-mediastinal involvement, namely right temporal fossa, cervical lymphadenopathy, as well as left breast and left axilla. Four (18.2%) had initial bone marrow infiltration. Initial central nervous system infiltration was recorded in two patients (9.1%). Patients affected by tumor lysis syndrome were successfully treated by usual conservative measures such as forced alkaline diuresis with furosemide and allopurinol, preceding or parallel to initial chemotherapy. Superior mediastinal syndrome was also successfully treated after starting cytotoxic treatment in all of the patients. Malignant pleural effusion enabled the diagnosis of LBL by flow cytometry in nine patients (40.9%). In other patients, the diagnosis was established by tumor biopsy. Other initial complications were noted in seven patients, namely: pericardial effusion in four patients; atelectasis, pneumothorax, and hematothorax in one patient each. Eight patients had LDH level above 500 U/L, and four patients above 1,000 U/L. Almost all patients (21/22) were diagnosed with T-LBL, while one patient had precursor B-LBL. Ten patients (45.4%) received previous glucocorticoid treatment in local/regional hospitals at some time during the four weeks before admission.

Nineteen patients (86.4%) achieved CR after induction treatment; one child (4.5%) achieved partial remission, while one patient died before achieving CR due to tumor lysis syndrome and consequent multi-organ failure. Another patient succumbed to a toxic complication (sepsis) during intensification treatment. The patient who achieved partial remission developed disease progression and died after second-line high-dose chemotherapy with radiotherapy and autologous stem cell rescue. One patient developed testicular relapse and was treated with second-line chemo-

Table 1. Patients' characteristics and outcome

Characteristics		N
Symptoms on admission	Difficulty breathing	12
	Tumor	9
	Cough	8
	Fever	7
	Pain	5
	Vomiting	2
	Weight loss	3
	Painful swallowing	2
	Sweating	2
Stage (total = 22)	I	0
	II	1
	III	14
	IV	7
Localization	Mediastinum	16
	Mediastinum + other localization	3
	Other than mediastinum	3
CNS		2
Bone marrow		4
Initial complications	Tumor lysis syndrome	3
	Superior mediastinal syndrome	13
	Pleural effusion	10
	Other	7
Treatment results	CR	19
	PR	1
	Death before CR	1
	Toxic death	1
Relapse	Local	0
	BM	0
	BM + CNS	0
	CNS	0
	Testicular	1
Secondary malignancy		0
Survival	OS	81.8%
	five-year pEFS	79.5%

LBL – lymphoblastic lymphoma; CNS – central nervous system; CR – complete remission; PR – partial remission; BM – bone marrow; OS – overall survival; pEFS – probability of event-free survival



Graph 1. Kaplan–Meier estimate of event-free survival for all evaluable patients (n = 22; median follow-up 91.5 months)

pEFS – probability of event-free survival

therapy and radiotherapy. This patient then progressed to develop the second relapse presenting with cutaneous and medullary infiltration and died due to cardiac failure after salvage therapy with nelarabine, without achieving another CR. Mean follow-up was 91.5 months (range 1.3–206.1, median 78.1 months). Five-year pEFS was 79.5% for all patients (Graph 1), while overall survival was 81.8%.

DISCUSSION

Analysis of clinical presentation, treatment results and survival of childhood LBL has not been previously published in Serbia. However, there are published single-center experiences of pediatric NHL, including patients with LBL [14]. All our patients, both children and adolescents, were treated in a similar way using BFM-based protocols for LBL.

General features of our patient group were similar to those described in larger patient series in the literature [13, 15]. The incidence of LBL is generally higher in boys than in girls, which was also reflected in our results (male to female ratio 2.6:1). Median age at diagnosis of LBL was comparable to published data. However, most of our patients were diagnosed with advanced stage disease and more patients were stratified to stage IV disease; also, there were more CNS-affected patients than expected from literature data. This may be due to the fact that symptoms of lymphoblastic lymphoma are not well recognized by primary care physicians, leading to late referral of patients. In our series, median time from presentation to diagnosis was about 30 days. In addition, misrecognition of symptoms leads to an unacceptable frequency of pretreatment by systemic glucocorticoids, further complicating the diagnostic process. In our series, as many as 45% of the patients were pretreated in this way. The heavy burden of disease could also be ascertained by the high percentage of patients (59%) with elevated LDH level of more than 500 IU/L. A high proportion of patients with superior mediastinal syndrome also supports this observation.

Three patients had tumor lysis syndrome as one of the initial complications. One of these patients died before reaching CR due to tumor lysis syndrome as well as septic complication and disseminated intravascular coagulation. Two other patients were successfully managed by conservative treatment; however, urate oxidase was not used since it is not available in Serbia.

Pleural effusion was present in 10 patients (45.5%). In nine of these patients (90%) we established the immunophenotypic diagnosis by flow cytometric analysis of effusion fluid. This diagnostic method offers a considerable advantage of being far less invasive than tumor biopsy [15], as well as the added benefit of reducing time to diagnosis, since results are available in a matter of hours.

The patients were treated according to the BFM-based protocols and stratified accordingly. Our results are comparable to those of other groups that use same or similar protocols. Five-year EFS of 79.5% is slightly inferior to the largest multicenter BFM study (85 ± 1%) [13]. We lost two patients during the initiation treatment, one of whom died of sepsis, and the other of TLS complications. This early mortality (9.1%) is certainly poorer than <6% that has been reported in developed countries [7, 16, 17]; however, it does not exceed reported early mortality in other countries with limited healthcare resources [18–21]. Social and economic conditions and living standards proved to be a significant factor that influences overall treatment outcome [22]. In spite of these difficulties, our results essentially do not fall behind those in developed countries.

CONCLUSION

Although inferior to leading international groups, our treatment results reflect a mostly favorable outcome in our patients affected by LBL. However, management of early treatment complications proves to be highly challenging in a country with limited financial and medical resources such as ours. Many patients were admitted and treated in a tertiary care institution with considerable delay, and some even received glucocorticoids in primary care centers prior to being referred, significantly compromising treatment success. In countries with poor socio-economic conditions, a well-considered balance between the intensity of systemic chemotherapy, avoiding unnecessary surgical procedures, and ability of timely and appropriate detection and treatment of early complications appears to be crucial for further improvement of treatment results. Additionally, improved education of primary health care physicians, as well as multi-institutional inter-disciplinary team efforts need to be strengthened in order to improve country-level data collection, treatment results and scientific research of pediatric LBL.

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REFERENCES

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Fourth ed. Lyon, France: IARC Press; 2008.
2. Dokmanovic L. Limfomi kod dece. In: Marisavljevic D, editor. Klinicka hematologija. First ed. Beograd: Zavod za udzbenike; 2012.
3. Uyttebroeck A, Suciu S, Laureys G, Robert A, Pacquement H, Ferster A, et al. Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: long term results of the EORTC CLG 58881 trial. Eur J Cancer. 2008; 44(6):840–6. [DOI: 10.1016/j.ejca.2008.02.011] [PMID: 18342502]
4. Eden OB, Hann I, Imeson J, Cotterill S, Gerrard M, Pinkerton CR. Treatment of advanced stage T cell lymphoblastic lymphoma: results of the United Kingdom Children's Cancer Study Group (UKCCSG) protocol 8503. Br J Haematol. 1992; 82(2):310–6. [PMID: 1419812]
5. Reiter A. Diagnosis and treatment of childhood non-hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2007:285–96. [DOI: 10.1182/asheducation-2007.1.285] [PMID: 18024642]
6. Márky I, Björk O, Forestier E, Jónsson OG, Perkkiö M, Schmiegelow K, et al. Intensive chemotherapy without radiotherapy gives more than 85% event-free survival for non-Hodgkin lymphoma without central nervous involvement: a 6-year population-based study from the nordic society of pediatric hematology and oncology. J Pediatr Hematol Oncol. 2004; 26(9):555–60. [PMID: 15342981]
7. Reiter A, Schrappe M, Ludwig WD, Tiemann M, Parwaresch R, Zimmermann M, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. Blood. 2000; 95(2):416–21. [PMID: 10627444]
8. Burkhardt B, Reiter A, Landmann E, Lang P, Lassay L, Dickerhoff R, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. J Clin Oncol. 2009; 27(20):3363–9. [DOI: 10.1200/JCO.2008.19.3367] [PMID: 19433688]
9. Dokmanovic L, Krstovski N, Vukanic D, Brasanac D, Rodic P, Cvetkovic M, et al. Pediatric non-Hodgkin lymphoma: a retrospective 14-year experience with Berlin-Frankfurt-Munster (BFM) protocols from a tertiary care hospital in Serbia. Pediatr Hematol Oncol. 2012; 29(2):109–18. [DOI: 10.3109/08880018.2011.652342] [PMID: 22376014]
10. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004; 127(1):3–11. [DOI: 10.1111/j.1365-2141.2004.05094.x] [PMID: 15384972]
11. Reiter A, Schrappe M, Parwaresch R, Henze G, Muller-Weihrich S, Sauter S, et al. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage--a report of the Berlin-Frankfurt-Munster Group. J Clin Oncol. 1995; 13(2):359–72. [PMID: 7844597]
12. Pession A, Masetti R, Rondelli R. Pediatric T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma therapy. Hematology Meeting Reports. 2009; 3(1):111–4.
13. Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005; 131(1):39–49. [DOI: 10.1111/j.1365-2141.2005.05735.x] [PMID: 16173961]
14. Pillon M, Piglione M, Garaventa A, Conter V, Giuliano M, Arcamone G, et al. Long-term results of AIEOP LNH-92 protocol for the treatment of pediatric lymphoblastic lymphoma: a report of the Italian Association of Pediatric Hematology and Oncology. Pediatr Blood Cancer. 2009; 53(6):953–9. [DOI: 10.1002/pbc.22162] [PMID: 19621432]
15. Mann G, Attarbaschi A, Steiner M, Simonitsch I, Strobl H, Urban C, et al. Early and reliable diagnosis of non-Hodgkin lymphoma in childhood and adolescence: contribution of cytomorphology and flow cytometric immunophenotyping. Pediatr Hematol Oncol. 2006; 23(3):167–76. [DOI: 10.1080/08880010500506354] [PMID: 16526117]
16. Tubergen DG, Krailo MD, Meadows AT, Rosenstock J, Kadin M, Morse M, et al. Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: a Childrens Cancer Group study. J Clin Oncol. 1995; 13(6):1368–76. [PMID: 7751881]
17. Patte C, Kalifa C, Flamant F, Hartmann O, Brugieres L, Valteau-Couanet D, et al. Results of the LMT81 protocol, a modified LSA2L2 protocol with high dose methotrexate, on 84 children with non-B-cell (lymphoblastic) lymphoma. Med Pediatr Oncol. 1992; 20(2):105–13. [PMID: 1734214]
18. Baez F, Pillon M, Manfredini L, Ocampo E, Mendez G, Ortiz R, et al. Treatment of pediatric non-Hodgkin lymphomas in a country with limited resources: results of the first national protocol in Nicaragua. Pediatr Blood Cancer. 2008; 50(1):148–52. [DOI: 10.1002/pbc.21046] [PMID: 16972240]
19. Fadoo Z, Belgaumi A, Alam M, Azam I, Naqvi A. Pediatric lymphoma: a 10-year experience at a tertiary care hospital in Pakistan. J Pediatr Hematol Oncol. 2010; 32(1):e14–8. [DOI: 10.1097/MPH.0b013e3181bdf1f3] [PMID: 20051771]
20. Müller J, Csóka M, Jakab Z, Ponyi A, Erlaky H, Kovács G. Treatment of pediatric non-Hodgkin lymphoma in Hungary: 15 years experience with NHL-BFM 90 and 95 protocols. Pediatr Blood Cancer. 2008; 50(3):633–5. [DOI: 10.1002/pbc.21144] [PMID: 17366531]
21. Gao YJ, Pan C, Tang JY, Lu FJ, Chen J, Xue HL, et al. Clinical outcome of childhood lymphoblastic lymphoma in Shanghai China 2001-2010. Pediatr Blood Cancer. 2014; 61(4):659–63. [DOI: 10.1002/pbc.24848] [PMID: 24243691]
22. Kent EE, Morris RA, Largent JA, Ziogas A, Sender LS, Anton-Culver H. Socioeconomic Impacts on Survival Differ by Race/Ethnicity among Adolescents and Young Adults with Non-Hodgkin's Lymphoma. J Cancer Epidemiol. 2010; 2010:824691. [DOI: 10.1155/2010/824691] [PMID: 20652048]

Лимфобластни лимфоми код деце – искуство једног центра у Србији

Јелена Лазић[1,2], Драгана Јанић[1,2], Нада Крстовски[1,2], Предраг Родић[1,2], Горан Милошевић[2], Срђа Јанковић[2], Димитрије Брашанац[1,3], Лидија Докмановић[1,2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетска дечја клиника, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

КРАТАК САДРЖАЈ

Увод Терапија нехочкинског лимфома (НХЛ) код деце заснована на интензивним протоколима лечења доводи до преживљавања без нежељених догађаја које се креће између 80 и 90%. Међутим, успех је нешто слабији у земљама у развоју. Лимфобластни лимфом (ЛБЛ) други је по учесталости тип лимфома код деце, чинећи око једне трећине свих НХЛ у детињству.

Циљ рада Циљ рада био је евалуација резултата лечења ЛБЛ у Универзитетској дечјој клиници (УДК) у Београду.

Методе рада Спровели смо ретроспективну анализу историја болести пацијената УДК код којих је постављена дијагноза ЛБЛ у периоду 1997–2015. године, уврстивши пацијенте узраста 0–18 година. У анализу је укључено укупно двадесет двоје деце.

Резултати Средњи узраст при дијагнози био је 10 година, уз преовладавање мушког пола. Сви пацијенти су лечени хемиотерапијом заснованом на протоколу Берлин–Франкфурт–Минстер (БФМ) за ЛБЛ. Уз средњу дужину праћења од 91,5 месеци, вероватноћа петогодишњег преживљавања без нежељених догађаја износила је 79,8% за све пацијенте, док је вероватноћа укупног преживљавања била 81,8%.

Закључак Иако нешто слабији од резултата водећих међународних група, наши резултати суштински одражавају задовољавајући исход лечења наших пацијената.

Кључне речи: педијатријски; лимфобластни лимфом; Србија; деца

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