Precursor B-cell Lymphoblastic Lymphoma in Children: Hacettepe Experience

Hilal Susam-Sen, MD, Bilgehan Yalcin, MD,† Diclehan Orhan, MD,‡ Burca Aydin, MD,† Nilgun Kurucu, MD,† Ali Varan, MD,† Aysegul Uner, MD,‡ and Tezer Kutluk, MD, PhD†*

Summary: The purpose of the study was to review the clinical and pathologic characteristics and treatment results of children with precursor B-cell lymphoblastic lymphoma. Of 530 children diagnosed with non-Hodgkin lymphomas between 2000 and 2021, 39 (7.4%) were identified as having precursor B-cell lymphoblastic lymphoma. Clinical characteristics, pathologic, radiologic, laboratory data, treatments, responses, and overall outcomes were recorded from hospital files and analyzed. The median age of 39 patients (males/females, 23/16) was 8.3 years (range 1.3 to 16.1). The most common sites of involvement were the lymph nodes. At a median follow-up of 55.8 months, 14 patients (35%) had a recurrence of disease (11 stage IV, 3 stage III); 4 were in complete remission with salvage therapies, 9 died of progressive disease and one died due to febrile neutropenia. Five-year event-free survival and overall survival rates were 65.4% and 78.3% for all cases, respectively. Survival rates were higher in patients with a complete remission at the end of induction therapies. The survival rates were lower in our study compared with other studies, which could be explained by the high relapse rate and higher incidence of advanced-stage disease due to bone marrow involvement. We demonstrated a prognostic impact of treatment response at the end of the induction phase. Cases with a disease relapse have poor prognosis.

Key Words: B-cell lymphoblastic lymphoma, children, treatment

(*J Pediatr Hematol Oncol* 2023;00:000–000)

Lymphoblastic lymphomas (LL) are high-grade neoplasms of the T- or B-lymphocyte precursor lineage and represent 25% to 30% of pediatric non-Hodgkin lymphomas (NHL).[1] Most LLs have T-cell phenotype and commonly present with advanced disease.[2] Pediatric precursor B-cell malignancies commonly present as B-cell acute lymphoblastic leukemia (B-ALL). Precursor B-cell lymphoblastic lymphoma (PBLL) is rare and makes up 20% to 25% of LLs.[3] Patients with PBLL have distinct clinical features as the most common sites involved are reported as the skin, lymph nodes, bones, and soft tissues; involvement of cerebrospinal fluid (CSF) is rare. Presenting signs and symptoms depend on the sites of involvement. Chemotherapy protocols designed for the treatment of pediatric ALL with a prolonged maintenance phase have been demonstrated to be effective in LBLs including PBLL.[2–4] In this study, we aimed to review our institutional experience with pediatric PBLL cases and review their clinical and pathologic characteristics, treatments, and outcome.

Received for publication September 20, 2022; accepted February 9, 2023.

From the *Division of Pediatric Hematology Oncology, Department of Pediatrics, Afyonkarahisar Health Science University School of Medicine, Afyonkarahisar; †Division of Pediatric Oncology, Department of Pediatrics; and ‡Department of Pathology, Hacettepe University Faculty of Medicine, Ankara, Turkey.

The authors declare no conflict of interest.

Reprints: Hilal Susam-Sen, MD, Division of Pediatric Hematology Oncology, Department of Pediatrics, Afyonkarahisar Health Science University School of Medicine, Afyonkarahisar, Turkey (e-mail: hilalsusam@hotmail.com).

DOI: 10.1097/MPH.0000000000002656

PATIENTS AND METHODS

The hospital files of all patients under 18 years of age diagnosed with NHL and treated between 2000 and 2021 were reviewed to identify those having PBLL. The demographic and clinical characteristics, disease sites involved, laboratory and histopathologic data, treatment, response to treatment, events in the follow-up, and final outcomes were recorded. The diagnoses were confirmed by histopathologic examination of tumor biopsies and immunohistochemistry and/or bone marrow examination complemented with flow cytometric analysis. At initial admission, all patients underwent complete physical examination followed by laboratory investigations including blood count, serum biochemistry, abdominal ultrasound and chest radiographs, computed tomography and/or magnetic resonance imaging of involved tumor sites, and also examination of bone marrow (BM) aspiration smears and CSF for staging purposes. The modified Murphy or St. Jude staging system was used to stage PBLLs.[5] In all treatment protocols, tumor response and remission status were evaluated at the end of the 1 week of cytoreductive chemotherapy, and also after completion of induction treatment, at regular points throughout the treatment period and after completion of the chemotherapy protocol. Complete remission (CR) was defined as complete regression of all initially involved tumor sites. Relapsed disease was defined as the recurrence of the disease after remission or after completion of therapy, detected by clinical examination and/or radiologic studies with confirmed pathologic examination when indicated.

All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 18.0, Chicago). The relationship between pairs of variables was examined by X^2 test. Overall survival (OS) and event-free survival (EFS) rates were calculated by the Kaplan-Meier method[6] and differences in survival were compared using the log-rank test. For EFS, an event was defined as no response to induction chemotherapy, local or metastatic relapse of disease, progression of disease under therapy, death irrespective of its cause, or secondary malignancies, whichever came first. For OS analysis, only death was taken into account. For both analyses time was censored at last follow-up date if no

failure was observed. The follow-up for all cases known to be alive was censored as of December 2021. In every instance, a *P*-value <0.05 was considered significant. The patients were followed after completion of treatment with regular intervals.

RESULTS

Between 2000 and 2021 a total of 530 NHL cases were diagnosed and treated at our department, and 39 (7.4%) had PBLL. Of 39 cases, 23 were boys and 16 were girls and their mean and median ages were 8 (± 4.2) and 8.3 years (range, 1.3 to 16.1), respectively. Fourteen cases had extranodal disease only, 7 cases had nodal disease only, and 18 had both nodal and extranodal disease. The most common sites of involvement were the lymph nodes followed by the bones, kidneys, the abdominal cavity, the intestines, the skin, and various other sites. Varying degrees of bone marrow involvement were detected in 21 cases (54%); information for the percentages of blastic involvement were not available in patient files. In 2 cases, CSF was positive for lymphoblasts. The clinical characteristics of the patients are given in Table 1. The disease stages according to the St. Jude staging system were as follows: stage I, 1; stage II, 2; stage III, 12, and stage IV, 23 cases.

The patients were treated according to different chemotherapy protocols between 2000 and 2021: from 2000 to 2002, 5 cases with LMB-89 and 1 with LMB-96 protocols;[7] from 2003 to 2019, 26 cases with LMT-89 protocol[8] and later 6 cases with the BFM-NHL protocol. One of the patients was referred to another hospital for treatment after initial diagnosis; the treatment details for this case was not known.

At the end of the induction, 30 patients had a CR of disease, the remaining 9 patients had partial remission. At a median follow-up of 55.8 months (range: 2.6 to 237), fourteen patients (35%) had disease recurrence (11 had stage IV and 3 had stage III disease). Eleven out of 14 patients with recurrence of disease were treated according to LMT-89 protocol and the remaining 3 were treated with LMB protocol at initial diagnosis. The median time to recurrence was 12 months (range: 2.6 to 33.9 mo). The sites of recurrence were as follows; isolated bone marrow disease in 10, extramedullary and bone marrow disease in 2, and isolated central nervous system (CNS) disease in 2 cases. None of the 4 patients with limited disease (stages I and II) experienced a recurrence of disease. Twelve patients were treated with ALL-REZ BFM protocol; BFM-90 protocol (plus radiotherapy) was used in one patient with isolated CNS relapse and information for the salvage therapy was unavailable in one patient. In 8 of 12 patients who received ALL-REZ BFM protocol, treatment was followed by an allogeneic stem cell transplantation; allogeneic stem cell transplantation was planned for 2 patients after the completion of ALL-REZ BFM protocol. FLAG IDA chemotherapy protocol (fludarabine, idarubicin, cytarabine) was administered for the latter 2 patients who were not in remission after ALL-REZ BFM protocol. Of 14 patients with a recurrence of disease, 4 were in CR with salvage therapy, 9 died of progressive disease. One patient died due to febrile neutropenia while receiving chemotherapy.

Five-year EFS and OS rates were 65.4% and 78.3% for all cases, respectively (Fig. 1). Five-year EFS and OS rates were significantly higher in patients with CR at the end of the induction treatments (EFS, $P < 0.001$; OS, $P < 0.001$).

TABLE 1. Clinical Characteristics and Treatment Protocols in 39 Children With Precursor B-cell Lymphoblastic Lymphoma

Characteristics	n (%)
Age (y)	
< 5	12 (30.8)
5-10	14 (35.9)
> 10	13 (33.3)
Sex	
Male	23 (59)
Female	16 (41)
Stages (St. Jude)	
I	1 (2,6)
II	3 (7.7)
III	12 (30.7)
IV	23 (59)
Nodal/Extranodal disease	
Nodal only	14 (35.9)
Extranodal only	7 (17.9)
Both nodal and extranodal	18 (46.2)
Sites of involvement*	
Lymph nodes	23 (59)
Bone marrow	21 (53.8)
Craniofacial bones	9 (23)
Kidneys	8 (20.5)
Abdominal mass	8 (20.5)
Multiple bones (other than the head)	6 (15.4)
Intestines	4 (10.3)
Scalp	2 (5.1)
Liver	2 (5.1)
Pancreas	2 (5.1)
Cerebrospinal fluid	2 (5.1)
Skin (gluteal, perianal)	1 (2.5)
Breast	1 (2.5)
Treatment protocols	
LMT-89	26 (66.6)
LMB-89	5 (12.8)
NHL BFM	5 (12.8)
BFM ALL	1 (2.6)
LMB-96	1 (2.6)
No data	1 (2.6)

*One patient may have ≥1 site(s) of involvements.

There was no significant impact of age, sex, lactate dehydrogenase levels, and disease stages on survival outcome. The EFS and OS rates based on the univariate analysis of clinical variables and treatment parameters are summarized in Table 2. The EFS and OS rates for cases with stages I-II-III cases were higher than those with stage IV disease, but this difference was not statistically significant (Table 2) (EFS, $P = 0.13$; OS, $P = 0.33$).

At the time of the study, 29 patients (74%) remained alive and 9 (23%) were dead, whereas 1 patient was lost to follow-up as of December 2021.

DISCUSSION

Precursor B-cell LLs are rare in children. The Children's Oncology Group (COG) protocol A5971 included 380 children with LL, 66 (17%) had PBLL, and majority presented with limited disease.[9,10] In the EURO-LB-02 protocol, 66/319 (21%) children with LL had PBLL (44% with limited disease) with a median age of 8.4 years (40 males, 26 females).[11] In our series, the median age and male predominance were similar to the reported pediatric LL series.[11]

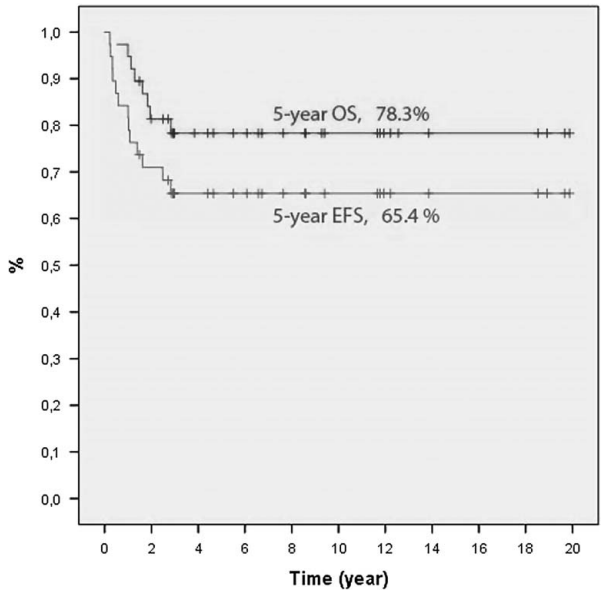

FIGURE 1. Event-free survival (EFS) and overall survival (OS) for 39 patients with precursor-B lymphoblastic lymphoma.

Patients usually present with limited disease, mostly involving skin, soft tissues, bone, or peripheral lymph nodes. In our study, extranodal sites were involved in most cases with or without nodal involvement. The most common sites of extranodal involvement were the bones followed by the kidneys and the intestines; skin involvement was not as common as reported in other series.[9,11,12] Neth et al reported that of 98 reported cases in the literature, ~75% had skin disease (with or without adjacent nodal disease), lymph node, bone, head and neck, and retroperitoneum involvement; mediastinal disease was uncommon.[12] Only 2 cases in our study had involvement of the CNS. CNS involvement was reported in <5% of the cases in the Euro-LB-02 protocol and in the series reviewing 98 children with PBLL.[11,12]

TABLE 2. Univariate Analysis for EFS and OS According to Clinicopathologic Characteristics

	n	5-year EFS (%)	*P*	5-year OS (%)	*P*
Age (y)					
≤10	26	65.2	0.9	80.2	0.5
>10	12	66.7		75	
Sex					
Male	23	60.6	0.33	73.2	0.33
Female	16	73.3		86.2	
LDH (IU/L)					
<500	25	71.2	0.21	83.2	0.31
>500	14	53.8		69.2	
Stages					
I-II-III	16	81.3	0.13	87.5	0.33
IV	23	54.5		72.1	
Remission status*					
CR	25	78.7	<0.001	89	<0.001
No CR	14	12.5		37.5	

*At the end of induction phase of treatment.
CR indicates complete remission; EFS, event-free survival; LDH, lactate dehydrogenase; OS, overall survival.

The modified Murphy or St. Jude staging system is used to stage PBLLs.[5] Only 10.3% patients in our study had limited-stage disease (stages I to II) and the rest (89.7%) had advanced disease (stages III to IV), contrary to similar studies which mostly reported limited disease in PBLL. Our hospital is one of the largest referral centers for children with cancer and this may explain the predominance of advanced-stage PBLLs who are often referred to comprehensive centers.

Precursor B-cell LLs and B-ALL are considered a spectrum of the same disease entity. The clinical distinction is based on the degree of bone marrow involvement, those with >25% blastic infiltration are designated as ALL, whereas those with a lesser degree of involvement are accepted as advanced-stage LBL with bone marrow disease.[2,4] In our series, 54% of patients had various degrees of bone marrow involvement. As information regarding the degree of BM involvement could not be obtained from the patient files, it was not possible to distinguish the cases who would be diagnosed to have stage IV PBLL or B-ALL in our series. Thus, all cases with BM involvement were classified as having stage IV disease. In a recent multicentric study, Kroeze and colleagues compared the clinical characteristics of PBLL and B-ALL. Most of the PBLL patients were diagnosed with advanced disease stage as in our study, and extramedullary localizations were more common.[13]

In both PTLL and PBLL clinical and genetic and molecular characteristics to be used for prognostic stratification are lacking due to small patient numbers. Patients are stratified based on stage alone in most treatment protocols as limited-stage disease and advanced-stage disease.[9,10]

It has been reported that EFS and OS rates do not depend on the patient's age or sex, or the response at the end of the cytoreductive pre-phase or induction.[14,15] In our series, EFS and OS rates were significantly higher for patients with a CR at the end of induction treatment which demonstrated the prognostic impact of treatment response.

For all LLs, an ALL-type therapy strategy has been demonstrated to be effective in many studies reported in the last 3 decades.[2–4,11,15–17] Thus, a similar strategy seems to be superior to a short-pulse B-NHL protocol for patients with PBLL.[11,12] As several cooperative group studies from both North America and Europe achieved survival rates over 90% in limited disease PBLL, subsequent studies aimed at decreasing anthracyclines and alkylator drugs as well as eliminating local and cranial irradiation.[3] All groups showed that dose reductions in limited disease are feasible. Current chemotherapy protocols utilized by the American and European cooperative groups do not use re-intensification phase in limited-stage disease PBLL patients.[2–4,9–11] For advanced-stage PBLL, chemotherapy protocols designed for the treatment of B-ALL are the preferred regimens which result in high survival rates. These are multiagent regimens derived from the BFM or LSA2L2 protocols which comprise induction, consolidation and prolonged maintenance phases.[2–4,10,11,15] Although treatment protocols were heterogeneous in our study, LMT-89 protocol was used for treatment in majority of the cases in our series which is an ALL-type therapy with an extended course of maintenance treatment.[8]

In our study, the 5-year EFS and OS rates were lower than those observed in other studies which ranged from 73% to 82% and 81% to 92%, respectively.[2–4,9–11,15] Two major problems concerning our patients seem to account for these

differences; the first being the higher incidence of advanced-stage disease with bone marrow involvement and the second being the higher relapse rate compared with other studies. In addition, the lack of molecular and genetic features may have contributed to the lower survival rates, as high-risk patients could not be identified. Relapses occurred in 14/39 (35%) patients, which is greater than in other studies where relapse rates ranged from 7.3% to 29.3%.[3,10,16,18] The higher relapse rate in our series seems to be due to the higher number of stage IV patients. Our results also revealed the poor prognosis of relapsed children. Of the 39 patients, 14 (35%) experienced a relapse and 9/14 died despite salvage therapies. This is consistent with published results.[3,18] The failure of the salvage therapies demonstrates the significance of effective first-line treatments in PBLL.

As mentioned earlier, the data for the exact extent of bone marrow involvement in our stage 4 patients were not available. This is a major limitation of this study. Some of our relapsed patients might have been considered as B-ALL relapses. So, it may not be appropriate to compare the survival rates for the stage 4 cases with other reported studies of PBLL.

Despite some notable limitations, we believe that our retrospective analysis of the patients with PBLL would add valuable information to the relevant literature for this rare subtype of pediatric NHLs.

REFERENCES

1. Burkhardt B, Hermiston ML. Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. *Br J Haematol*. 2019;185:1158–1170.
2. Minard-Colin V, Brugières L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. *J Clin Oncol*. 2015;33:2963–2974.
3. Ducassou S, Ferlay C, Bergeron C, et al. Clinical presentation, evolution, and prognosis of precursor B-cell lymphoblastic lymphoma in trials LMT96, EORTC 58881, and EORTC 58951. *Br J Haematol*. 2011;152:441–451.
4. Schmidt E, Burkhardt B. Lymphoblastic lymphoma in childhood and adolescence. *Pediatr Hematol Oncol*. 2013;30:484–508.
5. Murphy S. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphoma: dissimilarities from lymphomas in adults. *Semin Oncol*. 1980;7:332–339.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
7. Patte C, Michon J, Behrendt H, et al. Results of the LMB 89 protocol for childhood B-cell lymphoma and leukemia (ALL). Study of the SFOP (French Pediatric Oncology Society). *Med Pediatr Oncol*. 1997;29:358.
8. Bergeron C, Patte C, Leverger G, et al. Treatment of childhood lymphoblastic lym phomas. Results of the SFOP LMT 89 protocol. *Med Pediatr Oncol*. 1997;29:356.
9. Termuhlen AM, Smith LM, Perkins SL, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59:1229–1233.
10. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A 5971 trial: a report from the C hildren's O ncology G roup. *Br J Haematol*. 2013;162:792–801.
11. Landmann E, Burkhardt B, Zimmermann M, et al. Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma. *Haematologica*. 2017;102:2086–2096.
12. Neth O, Seidemann K, Jansen P, et al. Precursor B-cell lymphoblastic lymphoma in childhood and adolescence: clinical features, treatment, and results in trials NHL-BFM 86 and 90. *Med Pediat Oncol*. 2000;35:20–27.
13. Kroeze E, Arias Padilla L, Bakker M, et al. Pediatric precursor B-cell lymphoblastic malignancies: from extramedullary to medullary involvement. *Cancers*. 2022;14:3895.
14. Burkhardt B, Zimmermann M, Oschlies I, 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;131:39–49.
15. Mora J, Filippa DA, Qin J, et al. Lymphoblastic lymphoma of childhood and the LSA2-L2 protocol: the 30-year experience at Memorial Sloan-Kettering Cancer Center. *Cancer*. 2003;98:1283–1291.
16. Sandlund J, Pui C, Zhou Y, et al. Results of treatment of advanced-stage lymphoblastic lymphoma at St Jude Children's Research Hospital from 1962 to 2002. *Ann Oncol*. 2013;24:2425–2429.
17. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. *N Engl J Med*. 1997;337:1259–1266.
18. Burkhardt B, Reiter A, Landmann E, 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;27:3363–3369.