Acıbadem Univ. Sağlık Bilim. Derg. 2024; 15 (4)
https://doi.org/10.31067/acusaglik.1478940

Clinical Characteristics and Treatment Outcomes of Pediatric Patients with Non-Hodgkin Lymphoma: a Single-Center Experience From Southern Turkey

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ABSTRACT

Purpose: Non-Hodgkin lymphoma (NHL) accounts for 8-10% of all childhood cancers. In this study, we aimed to describe the epidemiological and clinical characteristics and treatment outcomes of pediatric NHL patients treated at a tertiary center.

Methods: The oncologic records of the patients diagnosed and followed up as NHL between 2013 and 2023 were reviewed retrospectively.

Results: A total of 36 patients were enrolled in this study. The most common pathologic subtype was lymphoblastic lymphoma (LL) (n=21, 58.3%) followed by Burkitt lymphoma (BL) (n=10, 27.8%), diffuse large B-cell non-Hodgkin lymphoma (DLBCL) (11.1%, n=4), and anaplastic large cell lymphoma (ALCL) (2.8%, n=1). Overall survival (OS) and event-free survival (EFS) were significantly longer in patients without bone marrow (BM) involvement (p=0.001 and p=0.02, respectively). EFS was significantly longer in patients without central nervous system (CNS) involvement (p=0.038). OS and EFS did not differ significantly according to NHL subtypes. There was no significant difference in OS according to age groups (p=0.7).

Conclusion: The OS with NHL has significantly improved. With the development of effective treatment regimens based on various pathologic subtypes, the result of pediatric NHL has significantly improved in recent years. The survival rates have reached >90%.

Keywords: cancer, pediatric, non-Hodgkin lymphoma

ÖZET

Amaç: Non-Hodgkin lenfoma (NHL), tüm çocukluk çağı kanserlerinin %8-10'unu oluşturur. Bu çalışmada üçüncü basamak bir merkezde tedavi gören pediatrik NHL hastalarının epidemiyolojik ve klinik özelliklerini ve tedavi sonuçlarını tanımlamayı amaçladık.

Yöntemler: 2013-2023 yılları arasında NHL tanısı konularak takip edilen hastaların onkolojik kayıtları geriye dönük olarak incelendi.

Bulgular: Bu çalışmaya toplam 36 hasta dahil edildi. En sık görülen patolojik alt tip lenfoblastik lenfoma (LL) (n=21, %58,3) olup bunu Burkitt lenfoma (BL) (n=10, %27,8), diffüz büyük B hücreli non-Hodgkin lenfoma (DLBCL) (n=4, 11.1%) ve anaplastik büyük hücreli lenfoma (ALCL) (%2,8, n=1) izledi. Genel sağkalım (OS) ve olaysız sağkalım (EFS), kemik iliği (BM) tutulumu olmayan hastalarda anlamlı derecede daha uzundu (sırasıyla p=0,001 ve p=0,02). Santral sinir sistemi (CNS) tutulumu olmayan hastalarda EFS anlamlı olarak daha uzundu (p=0,038). OS ve EFS, NHL alt tiplerine göre anlamlı farklılık göstermedi (p>0,05). Yaş gruplarına göre OS açısından anlamlı farklılık yoktu (p=0,7).

Sonuç: NHL'li hastalarda genel sağkalım gelişmeler oldu. Çeşitli patolojik alt tiplere dayalı etkili tedavi rejimlerinin geliştirilmesiyle, son yıllarda pediatrik NHL'nin sonuçları önemli ölçüde iyileşti. Hayatta kalma oranları >%90'a ulaştı.

Anahtar Kelimeler: kanser, pediatrik, non-Hodgkin lenfoma

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Received: 06.05.2024
Accepted: 26.07.2024

NHL is a group of lymphoid malignancies originating from the lymphoid tissues, mostly the lymph nodes. They often extend to other organs, including the spleen, bone marrow, or central nervous system. It is the second most frequent malignancy second among childhood cancers after leukemias, according to Türk Pediatrik Hematoloji Derneği (TPHD) and Türk Pediatrik Onkoloji Grubu (TPOG) cancer registry data. [1]. Compared to adult NHLs, pediatric NHLs are known to exhibit distinct clinical characteristics and distributions of pathologic subtypes. The NHL subtypes occurring in children are primarily high-grade tumors including BL, DLBCL, LL, and ALCL. Persistent weight loss, headaches, nausea, increased skeletal system edema and pain, and the presence of a lump or mass in the abdomen or cervical region are among the typical signs and symptoms. Radiological imaging, laboratory testing, and clinical evaluation are all part of the diagnosis process for NHL. The definitive diagnosis of NHL is made by histopathological and immunohistochemistry examination of the biopsy material. Administering biological subtype-directed chemotherapy is the key to success in childhood NHL as radiation and surgery have limited therapeutic benefits. In the current literature, available data on NHL among children in developing countries are limited. With the development of effective treatment regimens based on various pathologic subtypes, the result of pediatric NHL has significantly improved over the past thirty years [2]. The survival rates have reached >90% [3]. The purpose of this study is to assess the treatment modalities, results, and clinical and demographic features of our pediatric NHL patients treated in a single tertiary center in Turkey.

Methods

This study was approved by the Ethical Committee for Acibadem University, with the assigned decision no: 2024-6/233 and date: 18.04.2024. Data from children with NHL who were diagnosed and treated at the Acibadem Adana Hospital Pediatric Hematology-Oncology Department between 2013 and 2023 were analyzed. Patients with missing information or patients with blasts of 25% in BM were not included in this study. Retrospective analyses were conducted on the patients' age, gender, symptoms, physical examination results, complete blood count, lactate dehydrogenase concentration, histopathological features, stages at the time of diagnosis, treatments, and follow-up periods. NHL was diagnosed and classified according to the World Health Organization Classification of Hematological Malignancies [4]. A diagnosis of central nervous system disease was made if any of the following conditions were met: lymphoma cells in the CSF (> 5 cells/μL CSF), cerebral infiltrates on cranial MRI, or cranial nerve palsy. Radiotherapy was administered for central nervous system involvement-positive patients. LMB-96 chemotherapy regimens for BL and DLBCL; BFM-95 chemotherapy regimen for LBL; and modified BFM-NHL90 chemotherapy regimen for ALCL were used [5]. In the OS analysis performed according to age groups, patients were divided into three groups: 0-5 (n=4), 6-11 (n=15) and 12-18 (n=17).

Statistical Analysis

Data were analyzed using IBM SPSS V23. Descriptive statistics including frequencies and percentages for categorical (ordinal and nominal) data; and averages (means, medians, and/or ranges) and standard deviations used for all study variables. The OS and the EFS probabilities were calculated using the Log-rank and Kaplan–Meier method. The entire period of patient follow-up from the time of diagnosis was referred to as OS; EFS was defined as relapse, tumor progression, sepsis, or death from any cause from the time of diagnosis. p values of < 0.05 were considered statistically significant.

Results

A total of 36 patients with NHL were included in this study. Demographic and clinical of the patients' characteristics are summarized in Table 1. There were 23 boys (63.9%) and 13 girls (36.1%). The median age at diagnosis was 11.17±4.16 years. The most common pathologic subtype was LL (n=21, 58.3%) followed by BL (n=10, 27.8%), DLBCL (11.1%, n=4), and ALCL (2.8%, n=1). Most patients (66.7%) had advanced disease (stage III or IV) at diagnosis. Central nervous system (CNS) involvement and BM involvement were observed in 5 (13.9%) and 6 (16.7%) patients, respectively. In 13 (36.1%) of the patients, the primary site of the disease was the mediastinum, whereas in 12 (33.3%) abdomen, and 11 (30.6%) of the patients, it was cervical/peripheral lymph nodes. Various complications were observed at the time of admission to our hospital in four patients, one of which was tumor lysis syndrome, one was paralysis due to peripheral nerve compression, one was dyspnea due to a mediastinal mass, and one was "acute abdomen" from an intussusception. Patients were diagnosed via biopsy performed under general anesthesia. In a patient with a large anterior mediastinal mass, the diagnosis was made by tru-cut biopsy under local anesthesia. In another patient with pleural effusion, the diagnosis was made by pathological evaluation of the thoracentesis material.

Table 1: Patients' characteristics.

	(N: 36), n (%)
Age (yr)	11.17±4.16
Sex	
Male	23 (63.9)
Female	13 (36.1)
Pathologic subtype	
LL	21 (58.3)
BL	10 (27.8)
DLBCL	4 (11.1)
ALCL	1 (2.8)
B Symptoms	
Yes	23 (63.9)
No	13 (36.1)
BM involvement	
Yes	6 (16.7)
No	30 (83.3)
CNS involvement	
Yes	5 (13.9)
No	31 (86.1)
Primary site	
Mediastinum	13 (36.1)
Abdomen	12 (33.3)
Cervical/peripheral lymph nodes	11 (30.6)
St. Jude stage	
I	4 (11.1)
II	8 (22.2)
III	13 (36.1)
IV	11 (30.5)
Complication	
Yes	4 (11.1)
No	32 (89.9)
Relapse	
Yes	4 (11.1)
No	32 (89.9)
LDH level (IU/mL) %50 (%25-%75 percentiles)	258 (201-535)
Follow up time (yr) %50 (%25-%75 percentiles)	3 (2-5.75)

Abbreviations: BL, Burkitt lymphoma; LL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplasticlarge cell lymphoma; BM, bone marrow; CNS, central nervous system; LDH, lactate dehydrogenase.

Four patients relapsed at the primary disease site. Of these four (11.1%) patients who relapsed, two (5.5%) received chemotherapy and survived, one (2.7%) underwent auto-HSCT and survived, and one (2.7%) died due to disease progression after the salvage regimen. There was no difference between NHL pathological subtypes in terms of BM, CNS involvement, or advanced-stage status (Table 2). The mean follow-up time was 3.83±2.39 years (median 3 years). 5-year EFS was 77.8% and OS 91.7% (Figure 1, Figure 2). OS and EFS were significantly longer in patients without BM involvement (p=0.001 and p=0.02, respectively). EFS was significantly longer in patients without CNS involvement (p=0.038). There was no significant difference in OS in patients without CNS involvement compared to those with CNS involvement (p=0.739). All patients were divided into 3 age groups: 0-5 years (4 patients), 6-11 years (15 patients), and 12-18 years (17 patients). There was no significant difference in OS according to age groups and gender (p=0.7 and 0.774, respectively) (Figure 3 and Figure 4). OS, EFS, and LDH levels did not differ significantly according to NHL subtypes (p>0.05).

Table 2: BM, CNS involvement and disease extent at diagnosis according to pathologic subtype.

	LL n (%)	BL n (%)	DLBCL n (%)	ALCL n (%)	*p*
BM involvement					
Yes	3 (50)	2 (33)	1 (16)	0 (0)	0.871
No	18 (60)	8 (26.7)	3 (10)	1 (3.3)	
CNS involvement					
Yes	3 (60)	1 (20)	1 (20)	0 (0)	0.853
No	18 (58.1)	9 (29)	3 (9.7)	1 (3.2)	
Advanced disease (Stage≥3)					
Yes	15 (62.5)	6 (25)	2 (8.3)	1 (4.2)	0.658
No	6 (50)	4 (33.3)	2 (16.7)	0 (0)	

Abbreviations: BL, Burkitt lymphoma; LL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplasticlarge cell lymphoma; BM, bone marrow; CNS, central nervous system.

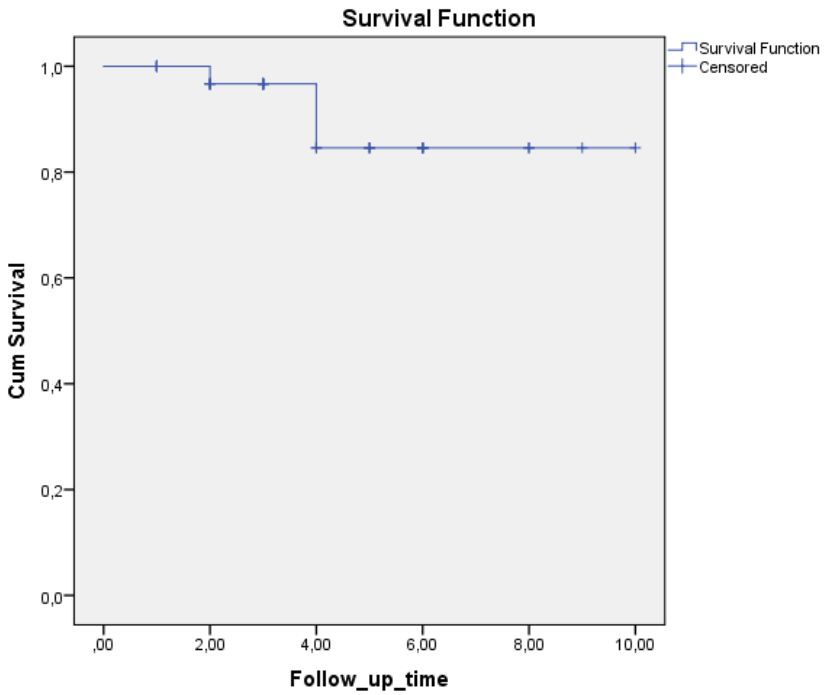

Figure 1: Kaplan-Meier estimate of overall survival (n=36; 5-year OS = 91.7 %).

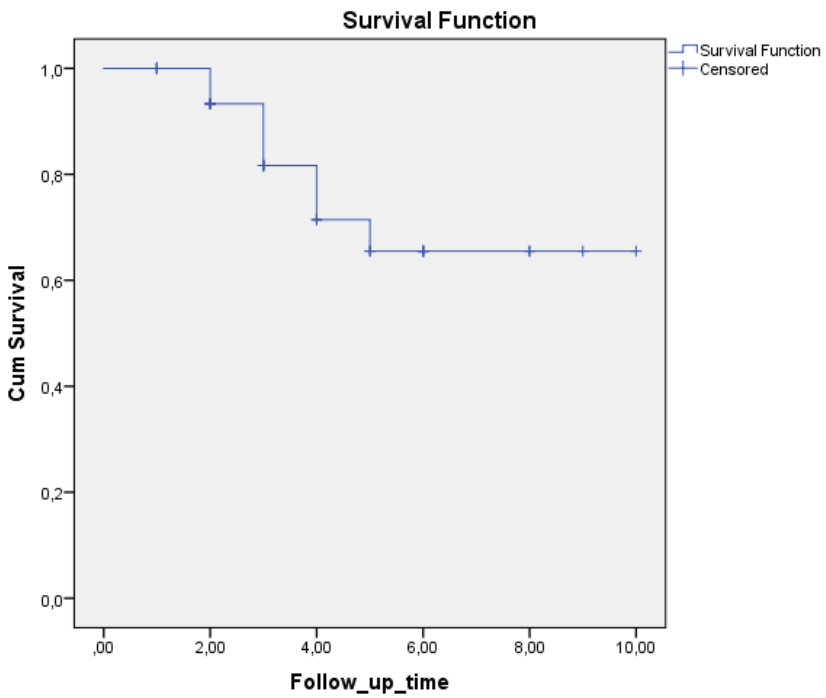

Figure 2: Event free survival (events: Mortality, progresyon, complication)

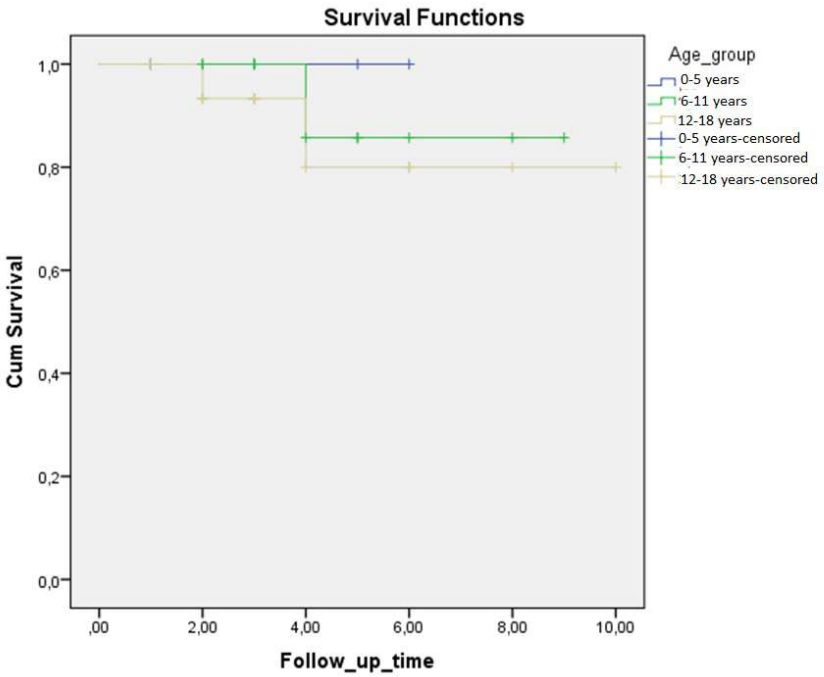

Figure 3: Figure shows OS according to age groups.

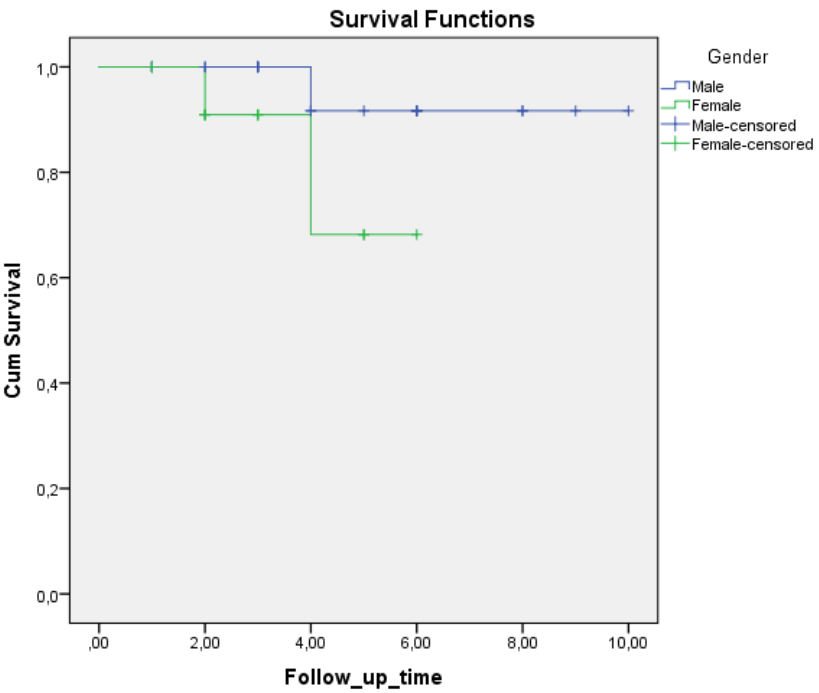

Figure 4: Figure shows according to gender groups.

Discussion

The second most prevalent childhood cancer is NHL, which even in children with advanced disease has a good long-term survival rate. Although the exact cause is unknown, infections, environmental stressors, immunodeficiency, and chronic inflammation are held responsible for etiology [6,7]. The prognosis for pediatric NHL has significantly improved during the last decades [8]. Improvements in treatment approaches, supportive care, and diagnostic techniques may be an explanation of this development. In the present study, we aimed to show the characteristics, treatment, and long-term follow-up of 36 children with NHL in a pediatric hematology-oncology unit in Turkey. The median age in our study was 11.1 years at diagnosis (ranging from 4 to 18 years). It is already known that the median age of presentation of NHL in childhood is 10 years. Cases involving children less than three are uncommon [9]. In a study conducted by Kara et al. with 80 children with NHL aged between 2 and 18, the median age was found to be 11.1 years, similar to our study [10] The most prevalent pathogenic groups in children are ALCL, DLBCL, LBL, and BL. Marginal zone, cutaneous, follicular, and peripheral T-cell lymphomas, which are common NHL subtypes in the adult population, constitute the remaining 10% of the whole [11]. When the distribution of subtypes of NHL in our patients was evaluated, LL was seen most frequently, contrary to the literature [12]. There were no patients diagnosed with the rare NHL subtype in our study. NHL in our study affected (63.9%) boys and (36.1%) girls with male to female ratio of 1.76. These findings support the male predominance of childhood lymphoma that has been previously established [13].

Rapidly growing tumors may exhibit symptoms specific to their size and location. Part of patient management is being able to deal with these complications alongside chemotherapy. One of our cases diagnosed with T-cell LL presented with hemiparesis in the right upper extremity due to nerve compression in the paravertebral region (Figure 5). In cases with such neurological deficits, immediate radiotherapy in addition to chemotherapy contributes positively to morbidity. It is suggested that field radiation involved may also be considered for palliation of pain or mass effect [14]. In addition, surgery has a limited role in treating NHL, although being crucial for the initial diagnosis, evaluating the presence of residual masses, and determining the efficacy of therapy. In our study, there were no patients who underwent surgery other than diagnostic purposes (palliative, etc.).

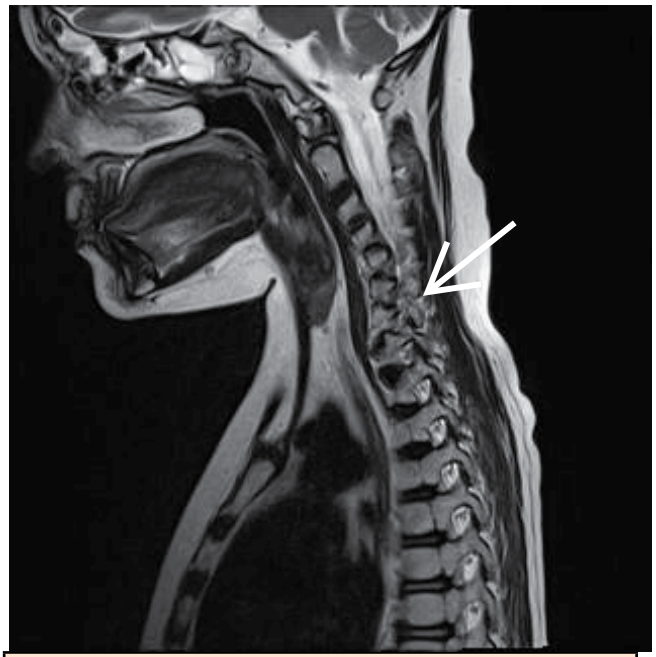

Figure 5: Contrast enhancement in leptomeningeal structures at the C4-C7 level in the cervical vertebrae (white arrow).

In the present study, 5-year EFS was 77.8% and OS 91.7%, respectively. With current treatment, children with Stages I to II disease have 2-year EFS rates of 85-98% and 85-90%, respectively. 85–90% and 85–90% 2-year EFS are seen in children with stage III and stage IV illness with BM involvement, respectively, and those with CNS disease (BL) have an 80% EFS [15]. Our retrospective study indicated that pediatric NHL patients responded well to our treatment approaches. The better treatment outcomes for pediatric NHL may have been brought about by the emergence of effective treatment regimens for various histologic subgroups. In our study, OS and EFS did not differ significantly by age and gender. In the retrospective study conducted by Karadoğan et al. with 47 children with NHL were treated with BFM-95 protocol. Four-year EFS, and OS was 78.7% and 80.8%, respectively, similar to our study [16]. Furthermore, in the cross-sectional retrospective study conducted by Sherief et al. with 142 children with NHL, regarding OS and EFS, there was no difference between gender and age [17]. However, the distribution of age and sex varied depending on the pathologic subtype and had distinct implications on treatment outcomes according to a BFM study on pediatric NHL [18]. In a recent study by Özdemir et al. with 65 children diagnosed with NHL (treated with NHL-BFM, ALL-BFM, and ALCL-99 protocols), the median follow-up time was 86.4 months and OS and EFS for five years were 94.6% and 90.3%, respectively. Relapse was observed in 6 (9.2%) patients, 4 of whom were at the

primary site [19]. In this heterogeneous disease group with many subtypes, larger patient groups and separate analyses for each subtype may be needed. BM and CNS involvement were rarely identified, although the majority of patients had advanced-stage diagnoses. However, in our series of patients, OS and EFS were significantly longer in patients without BM involvement. Compared to other subtypes, patients with BL and LL had higher rates of BM and CNS involvement. Consistent with our study, in the large cohort study conducted by Salzburg et al. with children and adolescents diagnosed with NHL, in 141 (5.9%) out of 2381 patients, CNS involvement was identified; it was more common in BL patients. Also, CNS involvement was associated with an advanced stage of NHL. EFS was 64%±5% and 86%±1% for the 112 CNS-positive patients and for the 1927 CNS-negative patients, respectively ($p < .001$) [20].

NHL patients who experience a relapse have a low probability of survival [21]. Only one (25%) of our 4 patients with relapse died due to disease progression following treatment with ifosfamide, carboplatin, and etoposide (ICE). In contrast to our results, in a recent study conducted with 639 relapsed NHLs in children and adolescents, the eight-year probability of OS was found to be 34 ± 2% [22]. This may be explained by the relatively small number of patients in our study. Moreover, one of our patients (LL) who relapsed underwent auto-HSCT using the conditioning regimen consisting of carmustine (BCNU), etoposide, cytarabine, and melphalan and survived. In a study with 36 relapsed and refractory pediatric patients with NHL who underwent allogeneic HSCT, OS at 3 years was 67% in all subtypes and 17% for LL [23]. In another study, a 5-year OS in relapsed cases was found 33% [24]. Furthermore, this suggests that traditional salvage regimens were not efficacious enough, and enhancing the survival rate is critically needed in relapsed and/or refractory NHL. Recent studies have shown that blinatumomab treatment and CAR-T cell-based immunotherapy appear to be promising treatment options for pediatric NHL patients [25,26].

Conclusion

In conclusion, the OS of children with NHL has significantly improved. More than 80% of children achieve long-term EFS with current treatments. In this study, we presented the clinical, demographic, and treatment results of the patients we followed for 10 years in a tertiary care center. Our results are comparable with the reports mentioned above. To better understand the biology and treatment of NHL, collaborative study is needed.

Declarations

Funding

This study had no external funding.

Conflicts Of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval

This study was approved by the Ethical Committee for Acibadem University, with the assigned decision no: 2024-6/233 and date: 18.04.2024.

Availability Of Data And Material

Data are available from medical records.

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