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PEDIATRIC NON-HODGKIN LYMPHOMA: TEN-YEAR EXPERIENCE WITH BERLIN-FRANKFURT-MUNSTER (BFM) PROTOCOLS FROM A TERTIARY CARE HOSPITAL IN TURKIYE

PEDİATRİK NON-HODGKİN LENFOMA: TÜRKİYE'DE ÜÇÜNCÜ BASAMAK MERKEZİ'NDEN BERLİN-FRANKFURT-MUNSTER (BFM) PROTOKOLLERİ İLE ON YILLIK DENEYİM

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Abstract

Objective: Progress in therapy of childhood non-Hodgkin lymphoma (NHL) is one of the stunning success stories of the past two decades. In developed countries, more than 80% of children with NHL can now be cured with modern therapy, even patients with widely disseminated disease. The aim of this study is to analyze all NHL patients who were treated in a single tertiary center in Turkiye.

Methods: An analysis of data of children with NHL, diagnosed and treated between 2003 and 2012 according to the original Berlin-Frankfurt-Munster (BFM) protocol in Kocaeli University Pediatric Oncology Department was carried out.

Results: Forty-seven children were eligible for analysis. Mean age at diagnosis was 9.6 years with a male: female ratio of 1.9. Thirty-one patients (66%) were mature B-cell NHL with 23 patients (48.9%) Burkitt lymphoma, 7 patients (14.8%) diffuse large B-cell lymphoma, one patient (%2) primary mediastinal large B-cell lymphoma; 13 patients (27.6%) were lymphoblastic lymphoma with 11 patients (23.3%) T-lymphoblastic lymphoma and 2 patients (4.2%) B-lymphoblastic lymphoma, and also 3 patients (6.3%) were mature-T cell lymphoma-anaplastic large cell lymphoma. Four-year event-free survival was 78.7% and overall survival was 80.8%.

Conclusion: These results with BFM protocol management reflect good treatment outcomes in our patients.

Keywords: Children, non-hodgkin lymphoma, Turkiye.

Öz

Amaç: Çocukluk çağı Non-Hodgkin lenfoma (NHL) tedavisindeki ilerleme, son yirmi yılın çarpıcı başarı öykülerinden biridir. Gelişmiş ülkelerde, NHL'li çocukların %80'inden fazlası, yaygın hastalık durumunda bile modern terapi ile tedavi edilebilmektedir. Bu çalışmanın amacı, Türkiye'de tek bir üçüncü basamak merkezde tedavi edilen tüm NHL hastalarını analiz etmektir.

Yöntem: Kocaeli Üniversitesi Pediatrik Onkoloji Anabilim Dalı'nda 2003-2012 yılları arasında orijinal Berlin-Frankfurt-Munster (BFM) protokolüne göre teşhis ve tedavi edilen NHL'li çocukların verilerinin analizi yapıldı.

Bulgular: Kırk yedi çocuk analiz için uygun bulundu. Ortalama tanı yaşı 9,6, erkek/kız oranı 1,9 idi. 31 hasta (%66) matür B hücreli NHL, bunların 23'ü (%48.9) Burkitt lenfoma, 7'si (%14.8) diffüz büyük B hücreli lenfoma, biri (%2) primer mediastinal büyük B hücreli lenfoma idi; 13 hasta (%27,6) lenfoblastik lenfoma, bunların 11'i (%23,3) T-lenfoblastik lenfoma ve 2'si (%4,2) B-lenfoblastik lenfoma ve ayrıca 3 hasta (%6,3) matür T hücreli lenfoma-anaplastik büyük hücreli lenfoma idi. Dört yıllık olaysız sağkalım %78,7 ve genel sağkalım %80,8 idi.

Sonuç: BFM protokolü uygulamasıyla elde edilen bu sonuçlar, hastalarımızda iyi tedavi sonuçlarını yansıtmaktadır.

Anahtar Kelimeler: Çocuk, non-hodgkin lenfoma, Türkiye.

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Introduction

Non-Hodgkin lymphoma (NHL) is caused by malignant transformation of lymphoid cells, the constituent cell of the immune system. It usually originates from the lymph nodes and tends to spread to organs such as spleen, bone marrow or central nervous system (CNS); primary bone or CNS presentations are rarely seen.[1] NHLs account for 60% of childhood lymphomas. It constitutes 8-10% of all childhood malignant diseases in developed countries. In recent years, an increase in adolescence has been reported.[2] The World Health Organization (WHO) classification from the International Lymphoma Study Group incorporates histology, immunohistochemistry, gene expression profiling, cytogenetic, molecular and clinical features for lymphoid neoplasms classification.

Childhood NHL is a widely high-grade and disseminated disease in contrast to adults where more than two-thirds of the tumors are indolent, low-grade malignancies and includes the four major subtypes; B- and T-lymphoblastic lymphoma (LL), Burkitt lymphoma (BL), Diffuse large B-cell lymphoma (DLBCL) and Anaplastic large cell lymphoma (ALCL) Commonly, enlarged lymphadenopathy due to the compression of surrounding structures cause clinical symptoms such as new onset wheezing, facial swelling, respiratory distress or acute abdominal pain, depending on the type of lymphoma and the areas of involvement. As the symptoms usually emerge rapidly (one to three weeks), efficient and appropriate handling of pathologic materials (tissue, bone marrow, cerebrospinal fluid (CSF) or pleural/ paracentesis fluid) is essential to ensure. Superior vena cava syndrome secondary to a large mediastinal mass obstruction, respiratory airway compression, tumor lysis syndrome (TLS) secondary to severe metabolic abnormalities from massive lysis of tumor cells requires immediate attention and emergency treatment.[3-5]

Combination chemotherapy is the primary modality used for the treatment of pediatric NHL. Some patients receive radiation therapy. Most children and adolescents with NHL have a good prognosis with current therapy. Long-term overall survival is achieved in >80 percent of pediatric NHL cases overall and in >90 percent of stage I or II pediatric NHL.

The aim of this study is to analyze all NHL patients who were treated in a single tertiary center in Turkey and present the results of Berlin-Frankfurt-Munster (BFM)-95 treatment protocol.

Methods

An analysis of data of children with NHL, diagnosed and treated between 2003 and 2012 according to the original BFM-95 protocol in Kocaeli University Pediatric Oncology Department was carried out. A total of 47 children, aged between 1 and 18 years old and who completed chemotherapy at least 2 years prior to the analysis, were included in the study.

The patients were evaluated regarding their ages, gender, symptoms, anatomical location of the tumor and histopathological characteristics retrospectively. Complete blood count and assessment of liver and renal function tests and serum LDH were performed. The diagnosis was made by histopathological evaluation of biopsies, bone marrow aspiration samples and for some patients, after clinical, radiological and cytological tests.

We classified our patients according to St. Jude's non-Hodgkin's lymphoma classification in children.[11] All patients were treated with BFM-95 treatment protocol. We calculated overall survival (OS) and event-free survival (EFS) for the patients. Overall survival was defined as the total follow up time of patients from the time of diagnosis; EFS was defined as relapse, tumor progression, secondary malignancy or death from any cause from the time of diagnosis.

SPSS 13.01 pack program was used for statistical analyses. Log-rank and Kaplan Meier tests were used for the evaluation of survival analysis. Statistically significant considered as $p<0.05$.

Results

A total of 47 patients were included in the study whose characteristics, primary localization and stage of the disease, diagnosis and the treatment results are summarized in Table **1**. The median age at diagnosis was 9.6 years with a male to female ratio of 1.9. According to subtypes, 31 patients (66%) were mature B-NHL with 23 patients (48.9%) BL; 7 patients (%14.8) DLBCL and one patient (2%) primary mediastinal large B-cell lymphoma (PMLBL); 13 patients (27.6%) were LBL with 11 patients (23.3%) T-lymphoblastic lymphoma (T-LBL) and 2 patients (4.2%) B-lymphoblastic lymphoma (B-LBL) and 3 patients (6.3%) were mature-T cell lymphoma-ALCL. Most patients, 36 (76.6%), were diagnosed in advanced stages, 24 (51%) stage III and 12 (25.5%) stage IV. Eleven patients (23.4%) had local disease; 2 (4.2%) stage I and, 9 (19.1%) stage II. Five patients (10.2%) had CNS involvement while 8 patients (%17) had bone marrow involvement.

Primary location of the disease was head and neck region in 17 (36%) patients while it was abdomen, mediastinum, peripheral lymph nodes and other (nasopharynx, bone, tonsil, CNS, sacral), 14 (30%), 6 (13%); 2 (4%) and 8 (17%) patients respectively. Thirty-seven patients (78.7%) were diagnosed via biopsy performed under general anesthesia. Six patients (12.7%) were diagnosed by examination of pleural fluid or ascites and 4 (8.5%) after bone marrow aspiration.

Two patients died of infections (4.2%); 6 patients (12.7%) died of disease progression and 1 patient (2.1%) died of secondary malignancy (glioblastoma multiforme). Eight patients (17%) relapsed; 7 of them were stage III and 1 of them stage IV during initial diagnosis. Median relapse time after diagnosis was 9 months (4-19 months). The mean follow-up time was 56 months (range 63±31, median 62 months). Four-year EFS was 78.7% and OS 80.8% Figure 1, 2.

Table 1. Patients Characteristics and Outcome in all NHL Patients

	LBL	B-NHL	ALCL	Total
	(n = 13) n	(n = 31) n	(n = 3) n	(N = 47) n (%)
Stage				
I	0	2	0	2 (4.2)
II	2	6	1	9 (19.1)
III	7	15	2	24 (51)
IV	4	8	0	12 (25.5)
Localization				
Abdomen	2	11	1	14 (30)
Mediastinum	5	1	0	6 (13)
Head and neck	6	10	1	17 (36)
Peripheral lymph nodes	0	2	0	2 (4)
Other	0	7	1	8 (17)
CNS	0	5	0	5 (10.6)
Bone marrow	4	4	0	8 (17)
Diagnosis				
Biopsy	8	26	3	37 (78.7)
Pleural fluid/ascites	3	3	0	6 (12.7)
Bone marrow	2	2	0	4 (8.5)
Treatment results				
Death due to disease progression	2	4	0	6 (12.7)
Death due to sepsis	1	1	0	2 (4.2)
Toxic death	0	0	0	0 (0)
Secondary malignancy	1	0	0	1 (2.1)
Survival				
OS	69.2%	81.3%	100%	80.8%
4-Year pEFS	69.2%	80.6%	100%	78.7%

Note. NHL = non-Hodgkin lymphoma; LBL = lymphoblastic lymphoma; ALCL = anaplastic large-cell lymphoma; B-NHL =mature B-cell lymphoma; CNS = central nervous system; OS = overall survival; EFS = event-free survival.

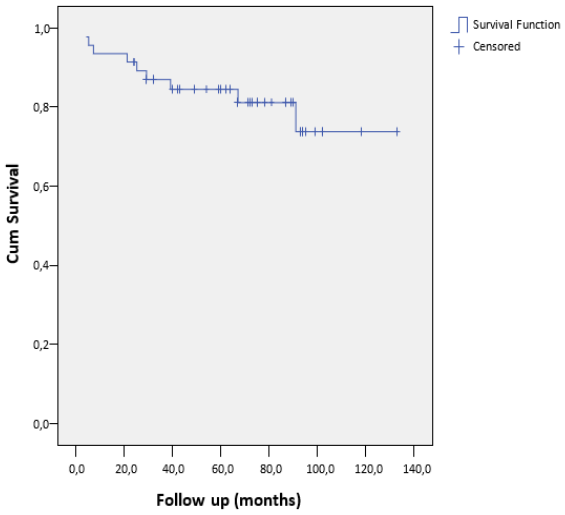

Figure 1. Kaplan-Meier estimate of overall survival. (n=47; 4-year OS = 80.8%).

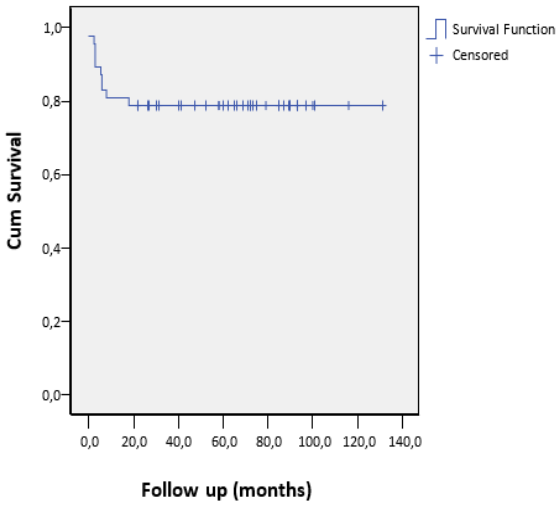

Figure 2. Kaplan-Meier estimate of event-free survival (EFS) (n=47; 4-year EFS = 78.7%)

Four-year EFS of male patients was 77.4% versus 81.3% for female patients Figure **3**, with no statistical significance (p >0.05).

All patients were stratified into 2 age groups: 0-10 years (23 patients) and 11-18 years (24 patients). The four-year EFS for these age categories was 78.3% and 79.2%, respectively Figure **4**, without reaching statistical significance (p=0.809).

Four-year EFS for different stages are shown in Figure **5**. Stage I and II survival was 100%: stage III 66.7% and stage IV 83.3%. Patients with stage I and II disease had significantly higher EFS compared to stages III and IV (p<0.05).

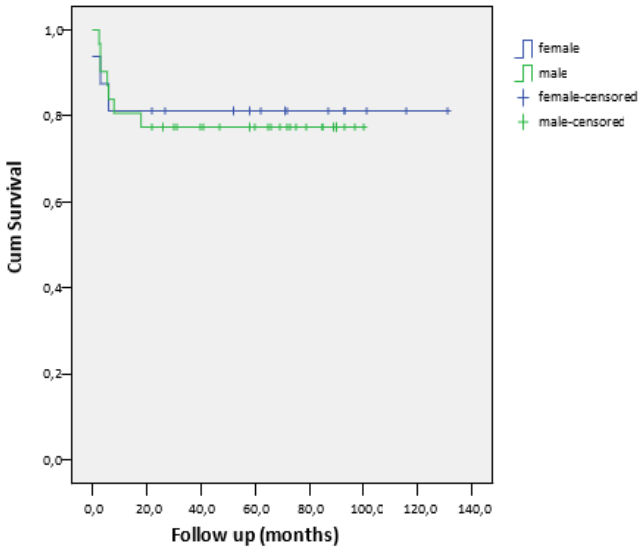

Figure 3. Kaplan-Meier estimate of event-free survival by sex; EFS = 77.4% versus 81.3% (P=0.809).

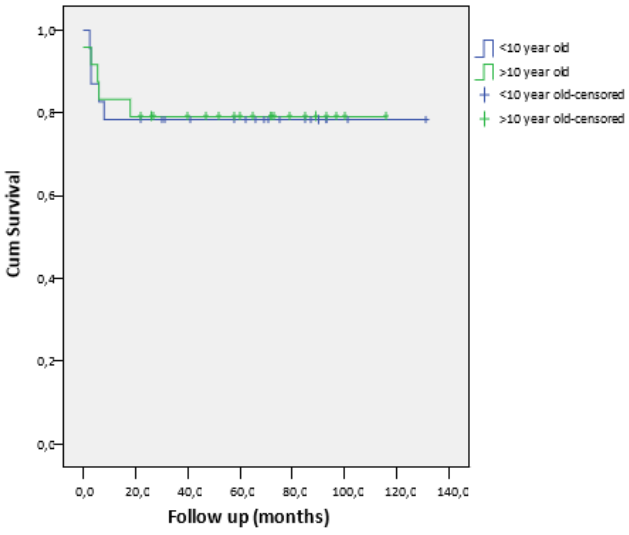

Figure 4. Kaplan-Meier estimate of event-free survival by age; EFS = 78.3% versus 79.2% (P=0.933).

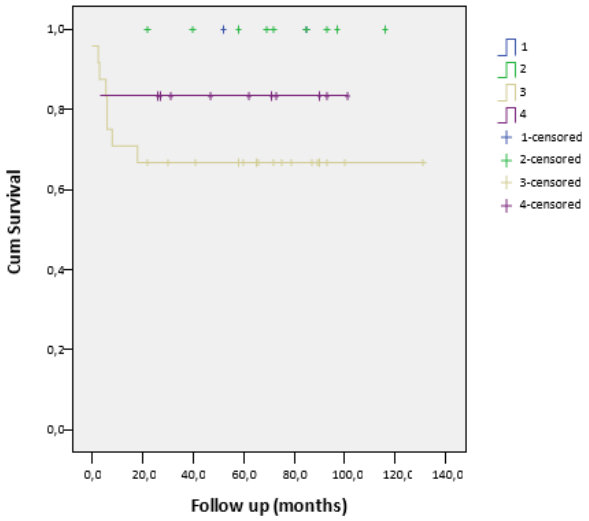

Figure 5. Kaplan-Meier estimate of event-free survival according to stage of disease (p=0.185).

The patient group with B-NHL included 23 children with BL, 7 children with DLBCL and 1 child with PMLBL. The age of the patients with BL ranged from 2.8 to 17, with a median of 11 years. Three patients had primary nasopharyngeal involvement, 2 patients had primary bone lymphoma, 1 patient had tonsillar lymphoma and 1 patient had primary CNS lymphoma. One of the patients died of sepsis and one of them relapsed 7 months after the end of treatment and had an autologous bone marrow transplant (BMT) but died of progressive disease. A patient who had an allogeneic BMT after relapse is still alive.

DLBCL patients aged between 2-15 years; median 11 years. One patient relapsed 9 months after the end of treatment and had an autologous BMT but relapsed again after BMT and died of progressive disease. A patient with DLBCL had no remission and died of progression. 17 years old boy diagnosed with PMLBL relapsed after 13 months and died of progressive disease. 4-year EFS was found 87% with BL and 71.4% with DLBCL.

Thirteen children were diagnosed with T-LBL and 2 with precursor B-LBL. The patients' ages ranged from 4.5 to 14.5; median 7.9 years; two of the patients died from progressive disease; one patient died from infections and one patient died from a secondary malignancy.

Three patients made up the ALCL patient cohort, one of whom was a 5-year-old girl who had isolated bone lymphoma when she was first diagnosed. Patients ranging in age from 4.5 to 14.5; the average age was 13 years. After treatment, there was no relapse or death. Figure 6 displays the NHL subtypes' four-year EFS.

Fourteen patients had liver toxicity, but no renal and cardiac toxicity was encountered. None of the patients died due to toxicity. Three patients had renal involvement while 1 patient had in pancreas, and another patient in adrenal gland. Ten patients had prophylactic cranial radiotherapy (pCRT). Two patients with primary bone lymphoma, 1 patient with primary mediastinal tumor and another patient with primary CNS lymphoma

received therapeutic radiotherapy (RT). RT was given to bone, mediastinum and bronchial region due to relapse of disease. Five BL and 4 DLBL patients were given rituximab.

Discussion

Because of the possible emergency complications of NHL, prompt recognition and therapy initiation at the time of diagnosis are critical. Children with NHL should be treated in a comprehensive pediatric oncology center with a multidisciplinary approach. In many series, there is a pronounced male predominance in all age groups[3,6] and the median age at diagnosis is around 10 years.[7,8,10] Demographics of our patients were as follows: male to female ratio 1.9/1 and mean age 9.6 years, median 10.4 years. The distribution of subtypes of NHL in our patients was concordant with WHO 2008 NHL Classification.[11] Burkitt lymphoma was the most diagnosed subtype, 48.9%; and the rates of DLBCL, PMLBL, LBL and ALCL were 14.8%, 2%, 27.6% and 6.3%, respectively.

No statistical difference was reached considering EFS in 2 different age groups and gender. Burkhard et al. showed the impact of gender and age on the outcome as there was a significant difference between NHL subgroups.[6] The reduced sample size in our study can be used to explain this outcome.

Diagnostic workup was made without histopathological confirmation in 10 patients (21%). Biopsy under general anesthesia should be avoided, if possible, especially in patients with significant airway narrowing or symptoms of respiratory distress.[12,13] Examination of bone marrow or pleural fluid/ ascites may be diagnostic.

The majority of patients, 36 (76.6%), had advanced stage disease, stage III in 24 (51%) and stage IV in 12. (25.5 percent). Almost 40% of children with NHL presented with stage I and II and the remainder with stage III and IV disease.[9] The frequency of patients with stage III/IV NHL was 49.4%. in China[14]; however, this frequency reaches 90% in Pakistan.[15]

Using stratification based on the biological aspects of the disease, patients were handled in accordance with BFM procedures. Four-year EFS was 78.7% and overall survival was 80.8%. Overall survival was 100% in stage I and II; while it was 66.7% in stage III and 91.7% in stage IV. Therefore, our results are similar to other study investigations using the same stratification approaches. EFS of 84.1% corresponds to the results of the largest multicenter BFM study.[6]

Death due to sepsis was encountered in 4.2 percent of patients and it is greater than the rate (2 percent) that has been recorded in developed countries but also lower than other countries rates with insufficient resources.[16,17] As a developing country, our outcomes do not linger behind the results that are reported in developed countries.

The survival outcome of children with B-NHL has noticeably improved through consecutive clinical trials in large study groups, and the cure rate of childhood B-NHL has reached 90% during the last two decades.[18-20] We showed a good survival outcome with 4-year EFS 80.6% in children with B-NHL, 87% with BL and 71.4% with DLBCL in the present study.

For LBL; the use of intensive protocols designed for children with ALL, such as the BFM regimens, have been shown to be more effective in advanced-stage disease.[21, 22] Our study showed 69.2% EFS with LBL.

Anaplastic large cell lymphoma (ALCL), within the classification of mature T-cell lymphoma, accounts for approximately 10-15 % of NHL in childhood. Event free survival achieves 70% of current treatment approaches using multiagent chemotherapy.[4,23] In our study, ALCL patients made up 6.3% of total with 100% overall survival.

CNS involvement was defined in 10.6% of patients and all had mature B-cell lymphoma. Pediatric studies have shown that CNS illness, particularly in more advanced stages of the disease, affects up to 6% of children with NHL.CNS involvement at diagnosis is not common but is most commonly seen in children with advanced BL and LL.[24] Our result was similar. Our research found that BM infiltration was 17%, which was a bit lower than rates in bigger NHL patient series.[6]

Conclusion

NHL was successfully treated in the majority of children in our clinic in which success depends on the type, stage and grade of the lymphoma. Better outcomes are associated with early diagnosis and localization of the disease in one region of the body. The clinical response to the treatment protocols was similar to the literature.

Ethical Approval

No ethics committee decision is required for the study.

Conflicts of Interests

The authors declare there are no conflict of interest.

Author Contribution

All authors contributed equally to this work.

Financial Disclosure

None.

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