

Prognostic factors and treatment results of pediatric Hodgkin's lymphoma: A single center experience

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The aim of this study was to assess the demographic, clinic data, prognostic factors and treatment/follow-up results of children who were diagnosed with Hodgkin lymphoma and followed in our center of Pediatric Oncology, Kocaeli University Medical Faculty, Kocaeli, Turkey, for 10 years.

This retrospective study evaluated 41 patients with Hodgkin lymphoma who were younger than 18 years-old. All patients were treated with risk-adapted ABVD (Adriamycin, Bleomycin, Vincristine, Dacarbazine) chemotherapy and also received involved field radiotherapy.

Thirty-two patients (78%) were males and 9 (22%) were females, with a mean age of 10.7 ± 4.0 years. The histopathological diagnosis was mixed cellular type in 51.2% of the patients. B symptoms (unexplained fever, unexplained weight loss, drenching night sweats) were present in 53.7% of the patients and 36.6% of the patients were at advanced stage at the time of the diagnosis. The 3-year overall and event-free survival rates were 88% and 5-year overall and event-free survival rates were 88%, 78%. Age, stage, treatment risk groups, presence of B symptoms and hematological parameters had no significant effect on overall and event-free survival in univariate analysis while bulky disease was the only significant factor on overall survival.

Our treatment policy was successful regarding the similar survival rates in the treatment risk groups, however novel treatment strategies adopting the early response with the reduction of adverse effects are planned in the near future.

Key words: child, Hodgkin lymphoma, risk group, survival, treatment

According to 2002-2008 data from the Turkish Pediatric Oncology Group (TPOG), pediatric patients with Hodgkin's lymphoma (HL) constituted 7.3% of all children with cancer¹. HL, the first cancer cured with treatment, is now treated with the combination of chemotherapy and radiotherapy and patients' event-free survival (EFS) and overall survival (OS) rate is 85-100%. We believe that each oncology center should determine the epidemiological characteristics of HL patients during certain time periods and compare their own treatment success rates with results reported in the literature, thus providing an opportunity to

evaluate treatment modalities. In this study, we evaluated the demographic and clinical features, risk-adapted treatment results, and prognostic factors that affect EFS and OS in HL patients that were treated in the past ten years in our center.

Material and Methods

A total of 41 patients under the age of 18 that received a histopathological diagnosis of Hodgkin's lymphoma and were treated and followed-up in our department of Pediatric Oncology, Kocaeli University Medical Faculty,

Kocaeli, Turkey, The years 2003 through 2012 were included in our study. Patients' epidemiological and demographic characteristics, as well as prognostic factors and treatment results were evaluated. Histopathological classification was done based on the World Health Organization (WHO) 2001 and 2008 hematopoietic and lymphoid tissue tumors classification^{2,3}, while the staging was determined based on the Ann Arbor classification⁴. At the time of diagnosis, all patients underwent lung radiography, abdominal ultrasonography, neck, chest or abdominal computed tomography, and magnetic resonance imaging of the abdomen or Ga-67 whole body scintigraphy for staging purposes. In thirteen patients diagnosed after 2008, the positron emission tomography (PET) scan was also used for staging. Laboratory tests included complete blood count, erythrocyte sedimentation rate, liver and kidney function tests, and serum lactate dehydrogenase (LDH) measurements.

All patients were treated with combined chemotherapy and radiotherapy. Primary chemotherapy ABVD (Adriamycin, Bleomycin, Vinblastine or Vincristine, Dacarbazine) regimen was administered in a varying number of cycles according to the stage or risk group (Table I).

The 6 MV or 18 MV linear accelerator devices were used in the radiotherapy treatment. The involved-field radiotherapy was used in patients that were evaluated based on the Ann Arbor classification system. The fraction dose was administered in the range from 150-180 cGy, with the total treatment dose varying between 20-25 Gy. The booster dose (average 5.4 Gy) of radiotherapy was given in the presence of bulky disease or recurrence.

The factors that could be relevant to survival and that were evaluated in relation to the

prognosis were the following: age, gender, living area, stage, histologic subtype, presence of bulky mass, presence of extranodal involvement, presence of B symptoms, hemoglobin (Hb) levels (<10 g/dl and ≥10 g/dl), leukocyte count (WBC <10,000/mm³ and ≥10.000/mm³), erythrocyte sedimentation rate (ESR <20 mm/h and ≥20 mm/h), and serum LDH (LDH: <500 IU/L and ≥500 IU/L).

Peripheral lymphadenopathy whose largest diameter was ≥ 5 cm and the presence of lymphadenopathy that was 33% greater than the widest intrathoracic diameter on the T₅₋₆ level in plain lung radiography were considered to be bulky disease.

Statistical Analysis

Numerical values were expressed as the mean (as a measure of central tendency) and standard deviation (± SD) for the distribution range of values. In the presence of extreme values, the median was used instead as a measure of central tendency of the variables. The differences between the frequencies of categorical variables were evaluated with chi-square (χ²) and Fisher's exact χ² test. The recurrence, progression, and the time until death from the start of the treatment or the time until the final assessment were used in defining the event-free survival, while the time until death from the start of the treatment or the time until the final assessment was used in defining overall survival. The Kaplan-Meier survival curves were used for survival analyses, the log-rank test was used for assessment of prognostic factors effective in survival, and the Cox regression test was applied for multivariate survival analysis. Relationships between the variables were investigated by using Pearson correlation analysis. All calculations were performed with SPSS 16.0 statistical software.

Table I. Treatment Schemes Applied to Patients

Risk group, stage	Treatment protocol	Number of patients (%)
Risk I, stage IA/B,IIA	2 cycles ABVD+20 Gy IFRT*	17 (41.5)
Risk II, stage IIB,IIIA	4 cycles ABVD+25 Gy IFRT	11 (26.8)
Risk III, stage IIIB,IVA/B	6 cycles ABVD+25 Gy IFRT	13 (31.7)

*IFRT: involved-field radiotherapy

ABVD, Adriamycin (25 mg/m² on 1st and 15th days), Bleomycin (10 mg/m² on 1st and 15th days), Vinblastine (6 mg/m² on 1st and 15th days) or Vincristine (1.5 mg/m² on 1st and 15th days), Dacarbazine (375 mg/m², on 1st and 15th days)

Table II. The Clinical and Demographic Characteristics of Hodgkin's Lymphoma Patients Characteristics All Patients

Total number of patients	41
Mean age (years) (\pm SD)	10.7 \pm 4.0
Age range (years)	3-18
Age groups	
\leq 10 years	17 (41.5%)
>10 year	24 (58.5%)
Histologic subgroups	
MC	21 (51.2%)
NS	15 (36.6%)
LR	1 (2.4%)
NLPHL	4 (9.8%)
Clinical Stage	
Stage I-II	26 (63.4%)
Stage III-IV	15 (36.6%)
Bulky disease	
Absent	31 (75.6%)
Present	10 (24.4%)
B symptoms	
Absent	19 (46.3%)
Present	22 (53.7%)
Extranodal involvement	
Absent	35 (85.4%)
Present	6 (14.6%)

NLPHL: Nodular lymphocyte predominant Hodgkin's lymphoma, MC: Mixed cellular, NS: Nodular sclerosis, LR: Lymphocyte-rich

$P < 0.05$ was considered statistically significant in all statistical evaluations.

Results

Thirty-two of our patients (78%) were male and nine (22%) were female (M/F=3.5/1). The mean age at the time of the diagnosis was 10.7 years old. Six of our patients (14.6%) were in the 0-5 age group, eleven patients (26.8%) were in 6-10 age group, twenty-two patients (53.6%) were in 11-15 age group, and two patients (4.8%) were in >15 age group.

Mixed cellular type (MC) was the most frequent (51.2%) histopathological subtype, followed by nodular sclerosing (NS) type (36.6%). The most common regions with involved lymph nodes were the cervical region (80.5%), the supraclavicular region (61.0%) and the mediastinal region (48.8%). Most of the patients (63.5%) were in early stages of the disease (stage I-II). The presence of B symptoms was detected in 53.7% of patients, the presence of peripheral and mediastinal bulky mass was observed in 24.4% and extranodal involvement was present in 14.6%. After diagnosis, all patients in the study group were followed for a median of 30 months (range, 6-120

months). The patients' clinical and demographic characteristics are shown in Table II.

There was no statistical difference in patients' WBC, Hb, ESR, and serum LDH between the stages. The patients' means and ranges of WBC, Hb, ESR, and LDH values at the time of diagnosis were 7.200 ± 5.500 (1,700-18,000), 11.21 ± 3.15 (7.5 to 13.4) g/dl, 36.00 ± 26.19 (3-107) mm/h, and 330.35 ± 161.44 (186-824) IU/L, respectively.

A complete response (CR) was achieved after two cycles of chemotherapy in all 17 patients from treatment risk group 1 (100%), in 9 patients from risk group 2 (82%), and in 10 patients from risk group 3 (77%). The overall CR rate achieved after two cycles of chemotherapy protocol in all patients was 88%. One patient from risk group 2 was diagnosed with progressive disease (PD) after two cycles of chemotherapy (stage IIB), while the other showed CR after four cycles of chemotherapy treatments. Thus, in risk group 2, the CR rate achieved after four cycles of chemotherapy reached 90%. On the other hand, two out of three patients from risk group 3 were radiographically defined as having a partial response (PR) after two cycles of ABVD

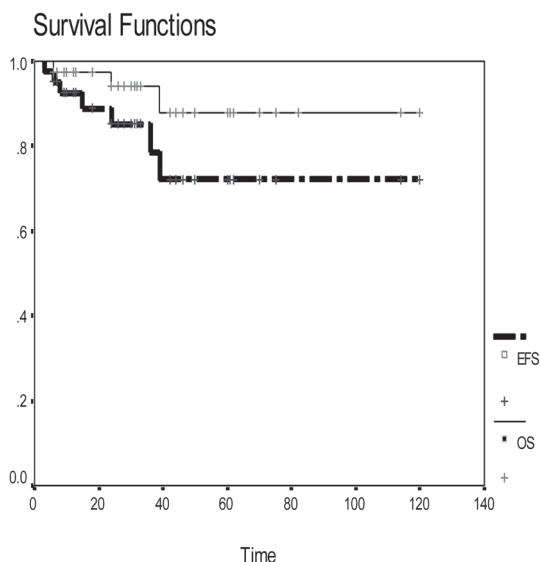


Fig. 1. Patients' overall and event-free survival rate

chemotherapy. In one of these patients, CR was achieved after four cycles of ABVD, while the other achieved CR after six cycles of ABVD. Therefore, in risk groups 3, the CR rate reached 85% after four cycles of chemotherapy and 92% after six cycles. Meanwhile, the third patient from risk group 3 was diagnosed with PD at the end of two cycles of chemotherapy (stage IVB). Thus, at the end of the chemotherapy treatment the CR rate in risk group 1 was 100%, in risk group 2 it was 90%, and in risk group 3 it was 92%.

For the entire study group, the CR rate was 95% and the PD was 5% following the chemotherapy treatment. Radiotherapy did not detect any changes in patients that responded to chemotherapy.

After the diagnosis, a recurrence was observed in five patients after a median of 23.8 months (range, 8-36 months). Following the treatment, complete remission was achieved in four of these patients, however one patient who was diagnosed with Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) that showed transformation to diffuse large B cell lymphoma (DLBCL) died due to infection during the febrile neutropenia period. Moreover, two patients that had normal follow-up periods were lost: one due to a traffic accident, and the other due to respiratory and cardiac dysfunction that developed as a result of lung infection.

No deaths were observed due to progression of the primary disease.

The 3-year OS and EFS rates of all patients were found to be 88% and 5-year OS and EFS rates of the patients were found to be 88%, 78% (Fig. 1).

The univariate analysis showed that factors evaluated in terms of prognostic significances such as age, stage, treatment risk group, B symptom, extranodal involvement, LDH, ESR, WBC, Hb levels, and socioeconomic status did not have any significant effects on OS and EFS. However, we determined that in patients with a bulky mass, the 3-year OS and EFS rate was 72%, significantly lower than the OS rate of patients without a bulky mass ($p = 0.032$). On the other hand, the multivariate analysis did not show any factors that had an effect on OS or EFS.

Discussion

According to the data from US Surveillance, Epidemiology, and End Results (SEER), Hodgkin's lymphoma constitutes 4% of annual cancer cases in the 0-14 years age group and 16.2% in the 15-19 years age group, making it the most common type of cancer in the older group⁵. Moreover, according to the 2002-2008 data from the Turkish Pediatric Oncology Group's Pediatric Tumor Registry system, lymphomas were seen in 19.6% of the 0-14 years age group and 23.2% of those in the 15-19 years age group, again making it the most common type of cancer in the older group. Of all the cases of cancer in the 15-19 years age group, 7.3% were diagnosed with HL¹.

The epidemiological characteristics of HL are different in developed countries compared to developing countries. While HL is mostly seen in the elderly population of developed countries, its first peak has shifted to the childhood period in developing countries^{6,7}. In our study, the majority (80.5%) of HL patients were in ≤ 14 years age group, which is similar to studies from different centers in Turkey and other developing countries. The studies from different centers in Turkey have reported the median age at the HL diagnosis to be 8, 7 and 6.5 years old, while in our study the median age of the patients at the time of HL diagnosis was 11 years old (range, 3-18 years)⁸⁻¹². Evaluation of HL's histopathological subtypes showed

that NS was the most common subtype seen in developed countries, while MC was the most frequently seen subtype in developing countries^{6,7}. Hodgkin lymphoma patients in the 15 year old or younger age group the male/female ratio was 3:1; in the adolescent age group, that ratio was 1.3:1, which is similar to adults¹³⁻¹⁵. Similar characteristics have been seen in studies conducted in different centers located in various regions of Turkey, however Büyükpamukçu et al.'s study⁹, which was the largest study and consists of data collected over more than thirty years, determined that epidemiological characteristics of HL patients were proportionally increased compared to epidemiological characteristics seen in developed countries. In Turkey, MC was the most common subtype (56%) of HL and the incidence of HL was approximately 3 times higher in males than females⁹⁻¹². In our study, the most common histologic subtype was also MC (21 patients (51.2%)) and the male to female ratio was 3.5:1. However, classification of the patients in terms of age groups revealed that the MC subtype was the most common subtype (12/17) in <10 years old age group, while the NS subtype was significantly more common (14/24) in > 10 years old age group ($p = 0.002$). In younger patients, the difference in histopathological subtypes seen in developed and developing countries might be associated with EBV infection¹⁶.

Nodular lymphocyte-predominant Hodgkin's Lymphoma (NLPHL) accounts for approximately 5% of all HL. Despite being classified as a form of HL in the Revised European-American Lymphoma (REAL) classification and in the WHO classification of lymphomas it differs in both histopathologic and clinical characteristics^{17,2,3}. It has long been recognized that large-cell lymphoma can occur either at diagnosis or as a subsequent relapse in patients with NLPHL^{18,19}. The relationship between NLPHL and DLBCL is incompletely understood and the incidence of transformation in patients with older than fifteen years old has been reported to range up to 17% and 30%^{20,21}. In our study, 4 (9.7%) patients (their age younger than fifteen years old) were diagnosed NLPHL and two patients experienced transformation to DLBCL (15 and 24 months after diagnosis). We think that pediatric oncology centers should evaluate the

frequency of transformation in their patients with NLPHL to DLBCL and compare their own treatment success rates, and perhaps together studies would be designed to give proper therapy to childhood patients.

According to SEER data, 19% of children are diagnosed with HL at stage I, 49% at stage II, 19% at stage III, and 13% at stage IV²². A study conducted in Hungary evaluated data from 30 years of records and reported that in the last decade, patients were most frequently (50%) diagnosed at stage II, while 40% of the patients were diagnosed at an advanced stage²³. The studies conducted in different centers in Turkey have shown an increase in the frequency of stage II disease, while the frequency of stage III disease has decreased. Early stage disease was detected in 55-58% of patients, while advanced stage disease was seen in 42-45% of the patients^{9,10}. The results of our study are also similar, with 63.5% of patients having early stage HL. The fact that nowadays the disease is being detected more frequently during early stages might be associated with an improved healthcare system and socio-cultural development.

In addition, SEER reported detecting B symptoms (one of the key features of clinical findings) in 39% of child and adolescent patients, while in Turkey that percentage was determined to be 30-40%^{9,10}. In our study, the frequency of detection of B symptoms was 53.7%, higher than the rate observed in other centers in Turkey. However, different studies conducted in other developing countries reported the frequency of B symptoms to be between 52-64%^{23,24}. In our study, the high ratio of patients that had B symptoms can be explained by the fact that only 15% of our patients were stage I, while the majority of them had advanced stage HL.

Although hematological and biochemical parameters show nonspecific changes in HL, such as the presence of anemia, ESR, and LDH levels were evaluated as prognostic parameters in a number of studies. These studies have shown that EFS is low in patients that had anemia, leukocytosis, or elevated ESR and LDH levels, but our study saw no indication of these parameters being poor prognostic factors^{9,10}. Moreover, in our study the assessment of these laboratory parameters in terms of effects on

prognosis did not allow for this comparison because of the our small number of patients.

Nowadays, the non-cross resistant chemotherapy has become a standard treatment approach and since the 1970's, various agents and combinations have been used²⁵⁻²⁷. In our study, we applied an ABVD chemotherapy scheme. Although this was a forced choice in our case, it provided the standard treatment and allowed the assessment of treatment success. We determined the risk adapted treatment approach based on stage, the presence of B symptoms, and especially the number of chemotherapy cycles.

Some studies have argued that when planning the risk adapted treatment approach, early-stage patients with bulky mass and extranodal disease should be treated as a medium risk group^{28,29}. Similarly, in our study one of our most important warnings while risk grouping was the additional assessment of the presence of bulky mass in risk group 1 and risk group 2. We determined that the presence of the bulky mass had negative prognostic effects on OS in particular. Meanwhile, the fact that extranodal involvement's effect on OS and EFS did not reach significance might be due to the small number of patients in that group.

Despite the successful treatment of HL, 2-15% of patients have relapse or refractory diseases³⁰. In a study conducted with 70 patients (age range 2.9-17.7 years) with relapsed or refractory SFOP (31 patients with refractory disease, 39 patients relapsed), the mean relapse time was determined to be 6 months (3-56 months)³⁰. In our study, relapse was seen in five patients (12%) and the median time of relapse was 23.8 months (range, 8-36 months).

Risk-associated treatments have been applied and various prognostic factors have been identified in order to reduce the long-term treatment and treatment-related toxicity in patients with good prognostic features and increase the survival of patients with poor prognostic features. However, there are only a limited number of studies on prognostic factors related to children. Numerous studies have determined that many factors have poor prognostic features on the overall survival rate, such as: male gender, advanced age, stage IIB, IIIB or IV disease, NS histological type, the presence of B symptoms, bulky mediastinal

mass, extranodal disease, the number of lymph nodes involved, Hb below 11 g/dl, leukocytosis and elevated ESR^{9,10,31,32}. Long term results of the German Pediatric Oncology Group's study of the German Society of Pediatric Oncology and Hematology-Hodgkin's Disease (GPOH-HD)-95 and GPOH-HD-2002 indicate that in low risk and early stage patients who did and did not receive radiotherapy both had excellent results (EFS, 93%)^{29,33}. The French Society of Pediatric Oncology group designed the MDH-90 study and this was based on chemotherapy regimen devoid of both alkylating agents and anthracycline, followed by 20 Gy of radiotherapy in early stage and good responders patients. Their 5-year EFS rate was 91%³⁴. North America pediatric oncology group (COG) had designed a lot of studies for children with favorable- intermediate- high risk HL. They used risk-adapted, response based chemotherapy protocols with or without radiotherapy. In several of the patients, positron emission tomography (PET) and computerized tomography (CT) was used for response evaluation. Their 5 year EFS rate was between 87-94%³⁵⁻⁴¹.

In our study, we only determined that in patients with a bulky mass the OS rate was significantly lower than in patients without a bulky mass. However, we found that the presence of the bulky mass lost its prognostic significance in multivariate analysis. This might have been because of the low number of patients and that the follow-up period was not suitable for this analysis. Alternatively, this situation could be a result of the successful treatment of many poor prognostic factors with combination therapy approach^{42,43}.

Although the approach applied in our center was successful, more studies that focus on early treatment response and reducing side effects without compromising treatment success are being planned.

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