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ORIGINAL ARTICLE

Clinical characteristics and treatment outcomes of pediatric Hodgkin lymphoma at a single center in Türkiye

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ABSTRACT

Objective: To review the 10-year experience of pediatric Hodgkin lymphoma at a single center in Türkiye.

Material and Methods: This study is a retrospective analysis of 82 pediatric Hodgkin lymphoma patients up to 18 years of age treated between 2009 and 2020.

Results: The mean age of the patients was 11 years (range 3–17 years), and 68% of the patients were male. The distribution of patients by stage was as follows: stage I, n=2 (2%); stage II, n=32 (39%); stage III, n=35 (43%); and stage IV, n=13 (16%). The trend in histopathology was predominantly mixed cellularity at 49%. The most common treatment protocol was ABVD (adriamycin, bleomycin, vincristine, doxorubicin), used in 83% of cases. The majority of patients (n=76, 93%) received involved-field radiotherapy following chemotherapy. Complete remission was achieved with first-line chemotherapy in 90% of cases. The 2-year overall survival (OS) and event-free survival (EFS) rates were 97.5% and 92%, respectively. There was no significant difference in OS and EFS in terms of gender, stage, and the presence of B symptoms.

Conclusion: Our data shows an excellent outcome for pediatric Hodgkin lymphoma, with results comparable to those of developed countries. Future studies should focus not only on treatment efficacy but also on identifying the best approaches to reduce long-term negative side effects.

Keywords: Child, developing country, Hodgkin lymphoma, outcome assessment.

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INTRODUCTION

In Türkiye, 2500–3000 new childhood cancer cases are expected each year. According to the Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Societies Registry, about 2000 new pediatric cancer cases are reported each year. The major cancers in children in Türkiye are leukemia (24.2%), lymphoma and other reticuloendothelial system (RES) tumors (18.5%), central nervous system (CNS) neoplasms (15.5%), neuroblastomas (8.2%), soft tissue sarcomas (7.2%), bone tumors (6.6%), followed by germ cell tumors, renal tumors, retinoblastoma, carcinomas-epithelial neoplasms, hepatic tumors and others. Lymphomas rank second in frequency as in many developing countries in contrast to West Europe or USA, where CNS neoplasms rank second in frequency.[1] Hodgkin lymphoma (HL) is eminently curable with the current treatment protocols. Long-term survival rates exceed 90% with chemotherapy with or without radiotherapy in children and adults.[2,3] Socioeconomic status is associated with the clinical and pathological features of this cancer. In developed countries, there is a bimodal age distribution, and HL is less common in children under 10 years of age. The population in Türkiye is relatively young. One-fourth of the population is younger than 15 years of age. According to the pediatric cancer registry in Türkiye 4446 (M/F: 2956/1487) pediatric lymphoma & other RES tumors cases have been reported between 2009–2021. Mixed cellularity type associated with Epstein Barr Virus (EBV) is most common in developing countries, the most common sub-type in developed countries is the nodular sclerosing (NS) type.[4] The very good treatment response and thus the expected life expectancy, especially in pediatric patients, has led to the modification of therapeutic regimens according to the disease staging and risk group in order to reduce toxicity exposure. Although the primary goal is survival, it is clearly important to minimize side effects, especially secondary malignancy and infertility, and this has led to the updating of treatment regimens, especially radiotherapy (RT).[5–9] As in other malignant diseases, the risk of relapse is higher in patients at advanced stage and who meet high-risk criteria at the time of diagnosis and has been shown to decrease two years after completion of treatment.[10] There are limited published data of HL treatment outcomes from developing countries. This study aimed to present the characteristics, treatment regimens, treatment responses and side effects, and survival data of pediatric patients diagnosed with HL in a tertiary care center from a developing country.

MATERIAL AND METHODS

Study Design and Patients

The data of the patients were collected retrospectively from patient file records and hospital electronic records. Patients under the age of 18 years who were diagnosed with biopsy-proven HL between November 2009 and January 2020 were enrolled in the study. Among 98 patients who were diagnosed within the specified time period, 16 were excluded from the study due to insufficient file information, failure to attend follow-up, discontinuation of treatment or going to another center, and missing data. The final study cohort included 82 patients. Clinical and demographic findings, histopathology results, positron emission tomography/computed tomography (PET/CT) scans for staging, and bone marrow biopsy results were collected. Pathological specimens were classified according to the WHO classification, and the modified Ann Arbor system was used for staging.[11] Bulky tumor was defined as any tumor with a diameter of ≥10 cm or widening of the mediastinum by more than one third of the maximum intrathoracic diameter on a chest radiograph. The presence of B symptoms was defined as fever above 38 °C lasting more than three days, night sweats, and >10% weight loss within six months. Stage I, IIA (without bulky disease and extranodal involvement) were defined as early stage, and IIB, III, and IV as advanced stages.

Treatment

Chemotherapy protocols that were used for HL patients were as follows: adriamycin, bleomycin, vinblastine, dacarbazine (ABVD); cyclophosphamide, vincristine, procarbazine, prednisone, adriamycin, bleomycin, vinblastine (COPP/ABV); mechlorethamine, vincristine, procarbazine, prednisone, adriamycin, bleomycin, vinblastine (MOPP/ABV); vincristine, etoposide, prednisone, adriamycin and cyclophosphamide, vincristine, prednisone, and dacarbazine (OEPA/COPDAC); and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP). The most frequently used chemotherapy regimen was ABVD, with 2–4 cycles of ABVD used in patients with early stage HL, while patients at advanced stages received six cycles or even eight cycles for selected patients. The majority of the patients received RT (14–25Gy) on the involved area. Ifosfamide, carboplatin, etoposide (ICE) chemotherapy protocol was given to relapsed patients, while gemcitabine, dexamethasone, cisplatin (GDP) or etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) chemotherapy protocols were used for treatment refractory patients, and autologous hematopoietic stem cell transplantation as well as brentuximab vedotin treatments were used for selected patients.

Outcome Definition

PET/CT was performed in all patients at initial diagnosis, at the end of treatment, and as an interim image modality in selected patients. Responses were categorized as: complete remission (CR) defined as the complete disappearance of the tumor and a negative bone marrow biopsy in patients with positive bone marrow involvement; partial response (PR) defined as a ≥50% decrease in tumor volume; progressive disease (PD) defined as a ≥50% increase in tumor volume or the appearance of new lesions.[12] Overall survival (OS) was defined as the time from diagnosis to death from any cause, and event-free survival (EFS) was defined as the time from diagnosis to first relapse, primary PD, or death from any cause.

Statistics

The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Inc., Armonk, NY, USA). Kaplan-Meier survival analysis was used to analyze EFS and OS. Potential prognostic factors (age, sex, B symptoms, clinical stages, and chemotherapy protocols) for OS and EFS were compared using the Cox regression test. Analysis results are presented as mean±standard deviation and median (minimum–maximum) for quantitative data, and as frequency and percentage for categorical data. A p-value<0.05 was considered statistically significant.

Ethics

The current study was approved by the Başakşehir Çam and Sakura City Hospital ethics committee (approval number 2022.04.106), and informed consent was obtained from the parents of the patients. The study was conducted in concordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

RESULTS

Clinical Characteristics

A total of 82 patients were enrolled in the study, of whom 56 (68%) were male. The median age at diagnosis was 11 years (range 3–17 years), and only 27 (33%) of the patients were in the early stage. Nearly half of the patients (43%) were included in stage III. Spleen involvement was present in 32% (n=26) of patients. The most common pathological subtype was mixed cellularity (49%), followed by NS (38%). EBV antigen was positive in 46% (n=38) of the tissue samples. Twelve (15%) patients had a bulky tumor at diagnosis, 29 (35%) had B symptoms. The most common presenting symptom was palpable lymph nodes (76%, n=62). Two (2.4%) patients were in the intensive care unit at the time of initial diagnosis, one of whom was intubated due to a mediastinal mass, and the other developed pericardial tamponade. One patient had underlying immunodeficiency (ITK deficiency) and chronic EBV infection. One patient was under follow-up with a diagnosis of neurofibromatosis, and one with a diagnosis of hemophagocytic lymphohistiocytosis.

Treatment and Outcome

The most commonly used protocol was ABVD, used in 68 (83%) patients, and most of these patients received four cycles (53%, n=36). Chemotherapy protocols other than ABVD were used in 14 patients (17%). Rituximab was added to the ABVD treatment of a patient who had a diagnosis of immunodeficiency. The majority of patients (n=76, 93%) received RT to the involved field at a dose of 14–25Gy, following chemotherapy. Two patients did not receive planned RT because one did not come to follow-ups, and the other was readmitted with relapse in the mediastinal region. Patients' clinical characteristics and treatment modalities are shown in Table 1.

When the treatment responses were evaluated, CR was obtained in 90% (n=74) of patients after chemotherapy. In the evaluation after the planned chemotherapy, PR was reported for 7.3% (n=6), and the chemotherapy protocols were extended for two or four more cycles, and CR was achieved in all of the end-of-treatment evaluations (n=80, 98%). The chemotherapy regimen was changed in 2.4% (n=2) patients with progressive disease. The first-line chemotherapy regimens for these patients were COPP/ABV and MOPP/ABV, and both patients received the ICE protocol as the second-line chemotherapy. The overall relapse rate was 7.3% (n=6). The median (range) relapse time was 25.5 (11–70) months. There was no difference between male and female gender in terms of relapse (p=0.834). Examining the salvage regimens used in relapse, ICE was primarily used in the first-line treatment in all of the relapsed patients. In addition, ESHAP and GDP were the other salvage regimens, and brentuximab was used in one patient (1/6). Autologous stem cell transplantation was performed in 4/6 patients.

Table 1: Patient's baseline characteristics

	Number of patients (n=82)	Percentage (%)
Age at diagnosis, years	median 11 (range 3–17)	
0–9 years	30	37
10–17 years	52	63
Male gender	56	68
Presenting symptoms		
Palpable lymph nodes	63	78
Mediastinal mass	18	22
Vena cava superior syndrome	1	1.2
Hemolytic anemia	1	1.2
Pericardial/pleural effusion	5	6
B symptoms*		
Yes	29	35
No	53	65
Bulky disease		
Yes	12	15
No	70	85
Stage		
I	2	2.4
II	32	39
III	35	43
IV	13	16
Histologic subtypes		
Nodular sclerosing	31	38
Mixed cellularity	40	49
Lymphocyte rich	6	7.3
Lymphocyte depleted	0	0
Unclassified	5	6
Treatment protocols (first line)		
ABVD	68	83
Other protocols	14	17
Chemotherapy+radiotherapy	76	93

*: The presence of B symptoms was defined as fever above 38 °C lasting more than three days, presence of drenching night sweats, and >10% weight loss within six months. ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine.

Three (3.6%) patients died, two due to pneumonia, one case of which developed immediately after RT and the other because of a second relapse. The median (range) follow-up time was 54.5 (3–144) months. The 5-year OS and EFS rates were 97.5% and 86%, and the 2-year OS and EFS rates were 97.5% and 92%

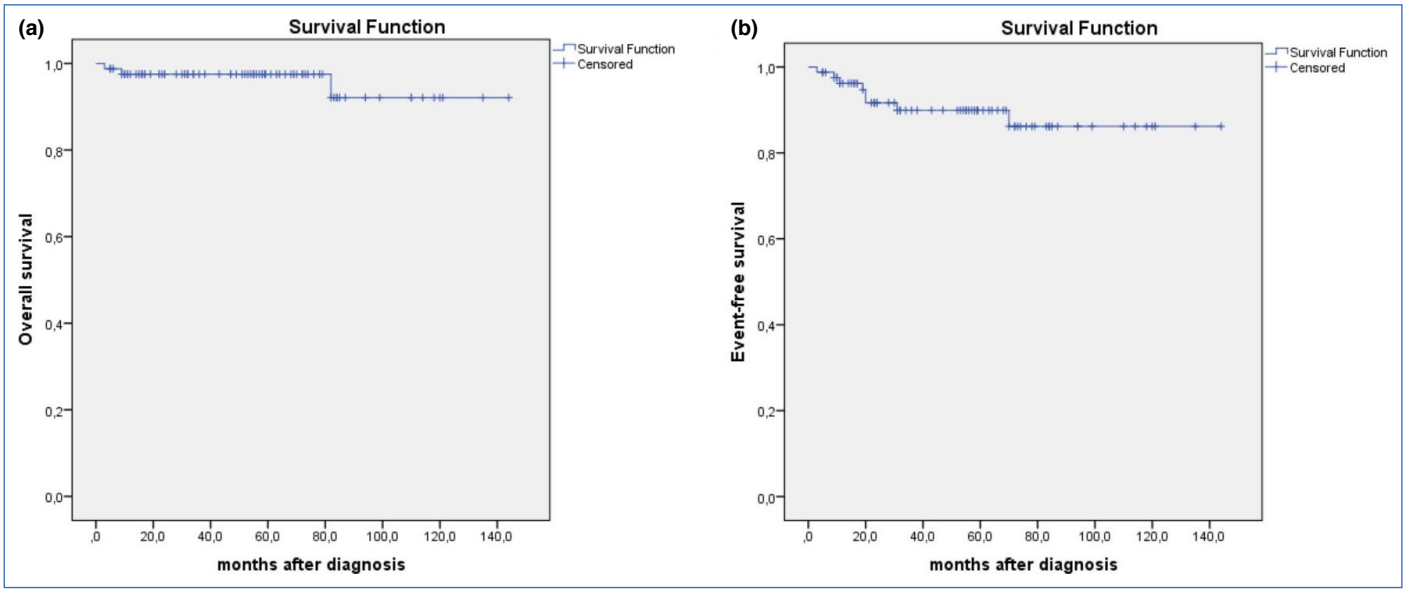

Figure 1: Kaplan–Meier curves of overall survival (OS) and event-free survival (EFS) for all patients (n=82).

(Fig. 1a, b). The 2-year OS and EFS for girls were 92% and 86.4%, and for boys were 94% and 92%, respectively, and were not different (p=0.082 and p=0.538, respectively). Comparing limited-stage patients to advanced-stage patients, the 2-year OS for early and advanced stages were 100% and 96%, respectively (p=0.186). The 2-year EFS for early and advanced stages were 100% and 85%, respectively (p=0.171). Comparing those who received ABVD to those who received other chemotherapy protocols, the 2-year OS was 97% for ABVD and 100% for other protocols, and the 2-year EFS was 93% vs. 75%, respectively, which was not significant (p=0.444 and p=0.079, respectively). Comparing those with B symptoms to those without B symptoms, 2-year OS and EFS were 100% vs 98% and 93% vs. 81%, respectively, and neither was significant (p=0.834 and p=0.107, respectively).

One patient developed Steven-Johnson syndrome with the COPP protocol, and the treatment was stopped and replaced with ABVD. Vincristine-induced neuropathy developed in 3 (3.6%) patients, but no neurological sequelae persisted after the end of treatment. Examining the long-term, treatment-related toxicities, thyroid dysfunction developed in 16% (n=13), and these patients were referred to endocrinology outpatients for follow-up. Since spirometry was not performed regularly, pulmonary toxicity could not be evaluated objectively, but none of the patients had pulmonary symptoms at follow-up, and cardiac toxicity and secondary malignancy did not develop in any patient during follow-up.

DISCUSSION

Studies into the treatment of HL, which was once almost invariably fatal but has become largely curable with the development of effective therapies, are ongoing. Treatment protocols and the duration of therapy are arranged according to the stage of the disease and the risk group, determined by the presence of a bulky tumor, B symptoms, and the extent of the disease.

Long-term complications secondary to treatment include gonadotoxicity, cardiovascular and pulmonary complications, thyroid disease, and other malignant diseases such as acute myeloid leukemia, myelodysplastic syndrome, or thyroid or breast cancer, although HL has an excellent life expectancy and treatment response.[13–16] Given these post-treatment complications, both pediatric and adult study groups, such as COG and Euronet HL groups, continue to investigate large numbers of patients to identify less toxic but equally effective regimens with satisfactory EFS and OS rates for HL. Improvements identified include the personalization of chemotherapy regimens according to patient risk group and treatment response, thus avoiding higher doses of chemotherapeutic agents, limiting the use of alkylating agents, and efforts to exclude procarbazine from protocols due to the risk of infertility. In addition, the fact that RT was initially applied to a larger area but is now generally limited to a narrower affected area and at lower doses, and even in the most recent studies, has been excluded from treatment in patients who receive effective chemotherapy and respond well to chemotherapy, even if they have advanced disease, have all signaled continuing optimization of HL treatments.[6,7,17–19]

In the present study, data were presented from a cohort of pediatric patients diagnosed with HL presenting to a single center between 2009 and 2020. The male sex was dominant, and the most common pathological subtype was mixed cellularity. These data are consistent with reports of pediatric HL in developing countries.[20,21] The most comprehensive study of pediatric HL patients from our country was conducted by Büyükpamukçu et al.,[4] which included 614 children and covered a period of 34 years. The male gender was dominant (approximately 4:1), mixed cellularity type was the most common form (344/614) followed by the nodular sclerosing type (90/614). The authors divided this long period into four periods, highlighting the outcome changes when comparing the earliest period with the latest. These changes included a shift towards the nodular sclerosing type over time (12.8% vs 35.2%, respectively), despite the mixed cellularity type remaining the most common subtype (54.1%

vs 42.6%, respectively). In the present study, the proportion of patients with mixed cellularity type was 49%. The authors noted that the median age at diagnosis also increased over time, from 8 to 9.25 years, and the proportion of patients younger than 4 years decreased from 9.5% to 5.6%. In the present study, the median age was 11.3 years, and the proportion of patients younger than 4 years was 4.8%. In addition, they reported that the best survival rates were achieved with the ABVD protocol compared to other chemotherapy protocols. In our study, the survival rates did not differ between ABVD and the other protocols used.

In a study from India, the most common pathological subtype was mixed cellularity (65%), the most commonly used chemotherapy regimen was COPP (73.5%), complete remission was achieved in 89% of the patients, and the relapse rate was reported to be 11%.[21] The authors stated that relapses were more common in the 11–14 age group, especially in patients with B symptoms, and that gender, histology, and stage did not appear to affect the rate of relapse. In our cohort, the mean age of patients with relapse was 11.8 years (142.5 months) and the mean relapse time was 26.6 months. In total, 5 of 6 relapsed patients were in advanced stages, and half of them (3/6) had B symptoms. Remarkably in their study, OS was not statistically different in the early and late stages; the only factor affecting OS was gender, and it was significantly higher in the male gender. In the present study, there were no significant differences in OS and EFS in terms of limited and advanced disease or gender.

The sensitivity of HL to many chemotherapeutic agents has led to the use of a variety of protocols for treatment. We used the ABVD protocol in most of our patients (83%). The use of ABVD means that patients receive a chemotherapy protocol every 15 days, do not require hospitalization, do not suffer from severe neutropenia, and that the treatment results are satisfactory, led to our preference for ABVD. There were no serious side effects in our patients. However, two of our patients died due to pneumonia, but in one of them, the ABVD protocol was completed, and pneumonia developed after receiving RT. Thyroid disease was the most common side effect in our cohort. ABVD-based chemotherapy is known to cause delayed cardiopulmonary side effects, especially with RT.[22] There were no patients who experienced cardiopulmonary side effects.

In an adult study, a protocol using an increased dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPescalated) and ABVD were compared.[22] The authors suggested that the treatment response with BEACOPPescalated was better, but risks including secondary myelodysplasia, leukemia toxicity, and infertility were more common.

Currently, one of the most important unanswered questions in the treatment of pediatric HL is the necessity of RT. Discussing the removal of RT from treatment plans is crucial to avoid secondary malignancies and side effects that may occur in organs such as the thyroid and lung.

Jain S, et al.[23] compiled data on patients who received ABVD and only bulky disease or partial response involved field RT (iRT) over 17 years. Remarkably, the results of those who did and did not receive RT during the continuation of ABVD treatment were similar. They suggested that the outcomes of especially early-stage patients were excellent and that risk factors at the time of diagnosis and PET-based treatment response should be considered to select the least toxic and most effective protocols.

In the current Euronet-PHL-C1 study on the role of RT in patients with HL, it was shown that the effect of RT was negligible in patients with intermediate and advanced stage disease who had a good treatment response.[19] Conversely, a systematic review argued that PFS was significantly reduced when RT was excluded from treatment based on PET/CT findings, suggesting that RT should remain a standard treatment after chemotherapy.[24] Additional evidence is needed to further refine the optimal treatment approach for HL.

In our study, 93% of patients received RT, and one of the two patients who did not receive RT due to non-compliance with the planned treatment experienced relapse in the mediastinum, the first involved field. Therefore, we suggest that the role of radiotherapy remains controversial, interim PET evaluation is crucial before discontinuing RT, and that PET/CT should be conducted meticulously and standardized.

CONCLUSION

According to our results, gender, limited or advanced stage, the use of the ABVD protocol and other chemotherapy protocols, and the presence of B symptoms did not differ at 2 years OS. When long-term treatment-related toxicities were examined, only thyroid dysfunction was detected. Most of the patients were treated with radiotherapy. These data are from our country; it is promising that the treatment outcomes and survival data are similar to those of developed countries.

The study has some limitations. Our study included a small number of patients. In addition, as the follow-up durations were relatively limited, the reliability of results concerning the occurrence of long-term side effects is somewhat reduced.

Statement

Ethics Committee Approval: The Çam and Sakura City Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.04.2022, number: 2022.04.106).

Author Contributions: Concept – EA, AA; Design – EA, AA; Supervision – EA; Data Collection and/or Processing – EA, ZK, SOA; Analysis and/or Interpretation – SAT; Literature Search – CB; Writing – EA; Critical Reviews – DT, GNÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

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