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Single-center experience of childhood Hodgkin lymphoma treated without radiotherapy

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ABSTRACT

Aim: Hodgkin lymphoma (HL) constitutes 40% of childhood lymphomas and approximately 6% of all childhood cancers. It is tried to achieve cure with combined treatment modalities consisting of chemotherapy, radiotherapy, monoclonal antibodies, and new treatment agents such as nivolumab. Radiotherapy-related infertility, secondary cancer, thyroid dysfunction, cardiovascular diseases, pulmonary fibrosis, and local skin reactions can be seen in the pediatric age group with a long life expectancy. In this article, pediatric patients diagnosed with Hodgkin lymphoma without the use of radiotherapy in the treatment were evaluated retrospectively and the survival results were reported as a single-center experience.

Material and Method: The patients with Hodgkin Lymphoma in the Pediatrics Hematology-Oncology Center at Erciyes University between January 2010 and December 2019 were included in the study and the data of the patients were evaluated retrospectively.

Results: In 68 pediatric patients with a mean age of 10.7 (±4.6) years, the male/female ratio was 1.3. The most detected finding at the time of diagnosis was cervical lymphadenopathy (83.8%). The most common mixed cellular subtype was identified (48.5%). Stage I-II disease was observed in 38.3% of the patients, and stage III-IV disease was observed in 61.7% of the patients. The median follow-up period of the patients was 61 (range, 8.3-161.6) months. Disease-free survival and overall survival were 85.3% and 94.1%, respectively. Treatment modalities to be used in this disease group, which has a high chance of cure after cytotoxic treatment, should be selected considering treatment-related long-term complications.

Conclusion: Acceptable good results obtained without radiotherapy are satisfactory and the chance of curative success will increase with the addition of new target agents to the treatment.

Keywords: Hodgkin lymphoma, children, radiotherapy

INTRODUCTION

Hodgkin lymphoma (HL) constitutes 40% of childhood lymphomas and approximately 6% of all childhood cancers (1). Hodgkin lymphoma generally shows a bimodal distribution, mostly in young adults and older people. Its incidence peaks at 15-35 years of age and above 50 years of age (2). While the most common subtype in developed countries is the 60-70% nodular sclerosing type, mixed cellular type is most common in developing countries (3). It is among the malignant diseases with the best long-term outcome with 80-90% cure rate after chemotherapy. Relapsed or refractory to treatment is observed in 15-20% of patients (4). It is tried to achieve cure with combined treatment modalities consisting of chemotherapy, radiotherapy, monoclonal antibodies and new treatment agents such as nivolumomab. However, treatment-related side effects should not be ignored. While radiotherapy is an important part of treatment in adults with HL, the risk-benefit ratio in children is discussed. Radiotherapy-related infertility, secondary cancer, thyroid dysfunction, cardiovascular diseases,

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pulmonary fibrosis and local skin reactions can be seen in the pediatric age group with a long life expectancy (2,3,5-7). In this article, pediatric patients diagnosed with Hodgkin lymphoma without the use of radiotherapy in the treatment were evaluated retrospectively and the survival results were reported as a single center experience.

MATERIAL AND METHOD

The study was carried out with the permission of Erciyes University Clinical Researchs Ethics Committee (Date: 11.12.2019, Decision No: 2019/854). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The patients younger than 18 years of age who were diagnosed with Hodgkin lymphoma in the Pediatrics Hematology-Oncology Center at Erciyes University between January 2010 and December 2019 were included in the study and the data of the patients were evaluated retrospectively. The data of the patients included in the study were obtained from the hospital electronic records and patient files.

In the study, demographic data of the patients, Hodgkin lymphoma subtype, presence of B symptoms, spread regions and stage of the disease, laboratory findings at the time of diagnosis, genetic study results, treatments and response to therapy, complications, relapse status, bone marrow transplantation and results, and prognostic factors were evaluated.

Patients Characteristics and Chemotherapy Protocols

The patients were diagnosed with HL by histopathological examination of biopsy samples. Bone marrow aspiration and biopsy, positron emission tomography/computed tomography (PET CT), and symptoms (fever, night sweats and weight loss) was used for staging of all patients. Before starting chemotherapy, the patients were staged according to Cotswolds modification of the Ann Arbor criteria (2).

Cyclophosphamide, vincristine, procarbazine, prednisone (COPP)/ doxorubicin, bleomycin, vinblastin, dacarbazine (ABVD) protocols were used alternately in the initial diagnosis. In early stage (Stage-1A and Stage-2A) HL patients, 2 cycles of ABVD and 2 cycles of COPP protocols were started, and the number of cycles was rearranged to a maximum of 4 for each protocol, according to the response to treatment. In advanced stage (Stage IIB, Stage-3 and Stage-4) HL patients, 3 cycles of ABVD and 3 cycles of COPP were started. According to the response to treatment, 4th cycle ABVD and COPP were given. At least 2 cycles of ifosfamide, carboplatine, etoposide (ICE) protocol were given in refractory or relapsed patients. Brentuximab was added to the treatment of refractory or relapsed patients diagnosed with HL after 2014. Autologous or allogeneic stem cell transplantation was performed in selected cases according to the underlying disease status such as immunodeficiency or relapse and refractory disease. No patient received radiotherapy.

Statistical Analysis

Descriptive statistics and quantitative variables were expressed as mean±standard deviation or median (minimum-maximum) according to whether the distributions were normal or not, using the Shapiro-Wilk test. Nominal variables were expressed as number of cases and percentage (%). The Kaplan-Meier method was used to estimate survival probabilities and the log-rank test for comparisons.

RESULTS

A total of 68 patients, 38 males (56%) and 30 females (44%) diagnosed with HL, were included in the study. Demographic data of the patients are given in **Table 1**. While HL is 3.3 times more common in boys than girls in the 0-5 age group, it is 1.5 times more common in boys in the 5-10 age group. In addition, the male-female ratio in patients older than 10 years is 0.9.

Table 1. Patient characteristics

Variable	Patient (n=68)
Median age (years)	10.7 (±4.6)
Gender (male/female)	38/30
Diagnosis of Patients	
Classical Hodgkin lymphoma (n=63)	
Nodular Sclerosis	27 (39.7%)
Mixed Cellularity	33 (48.5%)
Lymphocyte-rich	2 (2.9%)
Lymphocyte-depleted	1 (1.4%)
Nodular lymphocyte-predominant Hodgkin lymphoma	1 (1.4%)
Unknown subtype	4 (5.8%)
Diagnosis Staging	
Stage I	5 (7.3%)
Stage II	21 (31%)
Stage III	18 (26.3%)
Stage IV	24(35.4)
Disease Status	
Complete remission 1	56 (82.3%)
Relaps/refractory lymphoma	12 (17.6%)

Notes: Values are expressed as n (%).

The majority of our patient group consisted of patients with stage III-IV (61.7%). B symptoms were not observed in 45 patients. **Figure 1** shows the ratio of B symptoms according to the stages of the patients. As lymph node,

the most cervical lymph node involvement was observed (83.8%); in the extra-lymphatic system, the most spread to bone/bone marrow was detected (35.3%) (**Table 2**). Lymph node and non-lymph node involvements are summarized in **Table 2**. Bulky disease was detected in 10 patients (14.7%) and vena cava superior syndrome and/or upper mediastinal syndrome was detected in 8 patients (11.7%) at the time of admission. None of the patients had tumor lysis syndrome.

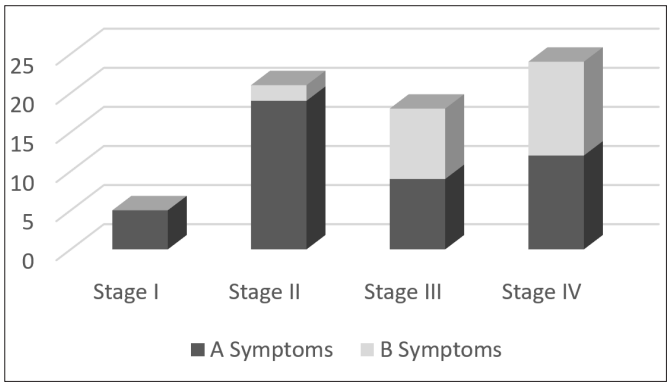

Figure 1. B Symptoms according to the stage of the patients

Table 2. Hodgkin lymphoma involvement sites

Site	Patient
Cervical LN	57 (83.8%)
Mediastinal LN	43 (63.2%)
Axillary LN	23 (33.8%)
Paraaortic LN	22 (32.3%)
Supraclavicular LN	19 (27.9%)
Parailiac LN	10 (14.7%)
Submandibular LN	7 (10.2%)
Inguinal LN	5 (7.3%)
Waldeyer ring	11 (16.1)
Spleen	23 (33.8%)
Bone/bone marrow	24 (35.3%)
Lung	10 (14.7%)
Liver	4 (5.8%)
Intestine	1 (1.4%)

Notes: Values are expressed as n (%).

STAT-6 mutation in 2 patients, CD27 deficiency in 1 patient, F-BAR domain only protein 1 (FCHO1) mutation in 1 patient, Interleukin-2-inducible T-cell Kinase (ITK) mutation in 1 patient, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD) mutation in 1 patient, Magnesium transporter 1 (MAGT1) deficiency, X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia (XMEN syndrome) in 1 patient were found in the genetic analysis of patients with relapse/refractory and reported in several publications (8).

Autologous hematopoietic stem cell transplantation was performed in 9 patients with relapse/refractory, and allogeneic hematopoietic stem cell transplantation was performed in 4 patients with immunodeficiency. One patient who was diagnosed with immunodeficiency and planned for allogeneic stem cell transplantation died due to sepsis. In addition, allogeneic stem cell transplantation is planned for 2 immunodeficiency patients.

The median follow-up period of the patients was 62 (range, 8.3-161.6) months. Disease-free (lymphoma, free) survival (DFS) and overall survival (OS) were 85.3% and 94.1%, respectively (**Figure 2 and 3**). While DFS was 96.2% and OS was 100% in patients with stage I-II, DFS was 76.2% and OS was 90.5% in patients with stage III-IV. One patient died of lymphoma progression, 2 patients died of sepsis after stem cell transplantation, and one patient died of sepsis secondary to immunodeficiency. Lymphoma-related mortality was 1.5% and overall mortality was 5.8%.

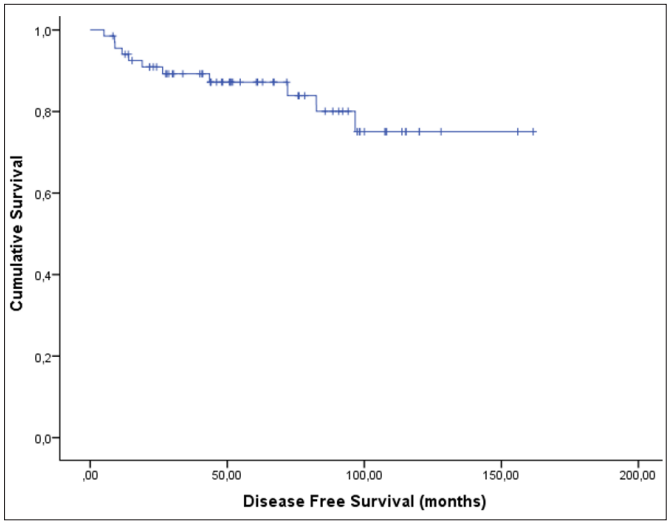

Figure 2. Disease-free survival graph of patients with Hodgkin lymphoma

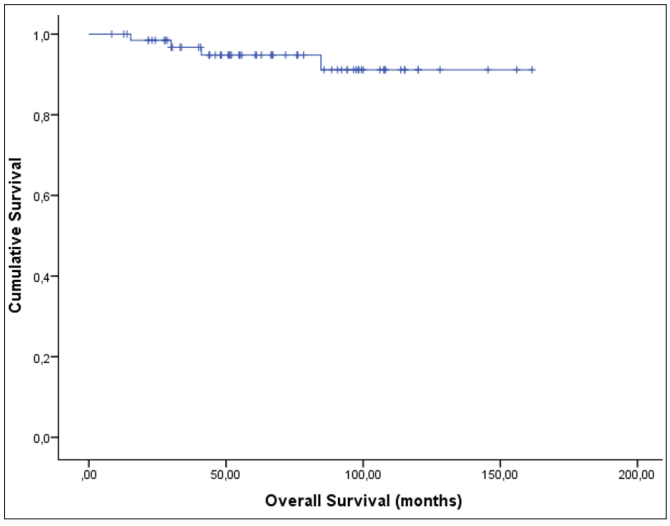

Figure 3. Overall survival graph of patients with Hodgkin lymphoma

DISCUSSION

Hodgkin lymphoma is a malignant disease of unknown specific etiology characterized by enlargement of lymph nodes. Conditions such as genetic diseases, socioeconomic status, positive family history, and Epstein-Barr virus (EBV) infection increase the risk of developing HL (2,9,10). In various studies, the age of incidence in the childhood age group is approximately 6-15.5 years. While Hodgkin lymphoma is more common between 5-10 years of age in developing countries, it has been found to be more common in children over the age of 10 in a study conducted in The United Kingdom (11-13). The mean age of the patients in our study was 10.7 (±4.6) years. 19.1% of the patients were aged 0-5 years, 26.4% were aged 5-10 years, and 54.5% were older than 10 years. The male/female ratio has been reported as 1.3-2.5 (13,14). 56% of our patients were male and 44% were female. The male to female ratio was 1.26, which is consistent with the literature. When we divide the patients into age groups, this ratio is; 3.3 in the 0-5 age group; 1.5 in the 5-10 age group, and 0.9 in patients older than 10 years old.

While nodular sclerosing type HL is observed at a rate of up to 80% in developed countries, mixed cellular type HL is observed at a rate of up to 60% in developing countries (12,13,15). In our study, approximately half of the patients diagnosed with HL (48.5%) were mixed cellular type, while the second most common (39.7%) type was nodular sclerosing type and these findings were comparable with other studies conducted in our country (16,17). The subtypes of the disease vary in relation to the development levels of the countries and the socioeconomic status of the people. Although the mixed cellular type was more common in our study, the incidence of nodular sclerosing type was seriously close to the incidence of the mixed cellular type. Generally, EBV is associated with mixed cellular HL lymphoma and is observed in young children, whereas nodular sclerosing type HL is more common in young adults and adolescents. Tumor cells are infected with EBV in 90% of cases in developing countries and 30% of cases in developed countries (18,19). EBV positivity was detected in tumor cells in 27 of our patients (39.7%).

Positron Emission Tomography (PET CT) is the standard imaging method for staging HL at the time of diagnosis and evaluating the response to treatment. However, it contains ionizing radiation. Nevertheless, in a study comparing magnetic resonance imaging and PET CT, PET CT was shown to be more sensitive in staging at the time of diagnosis and evaluating the response to treatment (20). We used PET CT for staging and evaluation of response to treatment in all of our patients.

Various combination chemotherapy regimens containing vinblastin, vincristine, dacarbazine, procarbazine, bleomycin, etoposide, cyclophosphamide, prednisone, doxorubicin, methotrexate are used in treatment (2). With the increase in survival rates, the focus is on eliminating or reducing the side effects that can be seen in long-term follow-ups. Studies are ongoing to reduce or eliminate anthracyclines due to its cardiotoxic effect, procarbazine for infertility, and radiotherapy due to its multiple side effects . In the studies of Dana Farber and St Jude Consortium, Children's Oncology Group (COG), and the German Society of Pediatric Oncology groups in low-risk patients who received radiotherapy, overall survival and event-free survival were 96.1-100% and 86-95%, respectively. In the studies of COG and the German Society of Pediatric Oncology group, overall survival and event-free survival were 93-98% and 82-94% in patients with medium and high-risk group HL who received radiotherapy (21). In a study using radiotherapy, in which patients with 43.1% early-stage disease and 55.9% advanced-stage disease, 5-year overall survival, and event-free survival were 96.6% and 84.7% respectively (12). In another study in which early-stage 92 patients and advanced-stage 104 patients did not use radiotherapy, 5-year overall survival and event-free survival were found to be 89.6% and 82.1%, respectively (3). Mixed cellular lymphoma was the most common subtype in both studies (3,12). In our study, 38.3% were evaluated as early-stage and 61.7% as advanced-stage. In the early and advanced patient group, 5-year overall survival is 90%.

Autologous hematopoietic stem cell transplantation following high-dose chemotherapy is the standard treatment approach in relapsed and refractory patients. In the study, which included 38 pediatric patients with a diagnosis of HL, 10-year survival and event-free-survival were 71.4% and 67.1%, respectively (22). Allogeneic stem cell transplantation can be performed in relapsed cases after autologous stem cell transplantation or in HL that develops on the basis of disease such as immune deficiency (9,10). In the meta-analysis, overall survival and relapse-free survival after transplantation were 50% (41-58) and 31% (25-37) (21). One of our patients who underwent 10 autologous and 4 allogeneic stem cell transplants died due to post-transplant relapse and 2 died due to sepsis.

Although it varies depending on the stage of the disease in various studies, the total relapse rate has been reported as 11.2-30.4 (11,12,23,24). Relapse is observed in 10% of patients with early stage HL and 25% in those with advanced stage HL after first-line treatment (25,26). The relapse rate was found to be 14.7% in our patients. In relapsed and refractory cases, especially if the age of diagnosis is under 5 years, genetic studies are recommended to investigate diseases predisposing to lymphoma (9,10).

CONCLUSION

Treatment modalities to be used in this disease group, which has a high chance of cure after cytotoxic treatment, should be selected considering treatment-related long-term complications. Acceptable good results obtained without radiotherapy are satisfactory and the chance of curative success will increase with the addition of new target agents to the treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researchs Ethics Committee (Date: 11.12.2019, Decision No: 2019/854).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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