Outcome of 102 patients under 5 years of age with Hodgkin lymphoma

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ABSTRACT

Background. Hodgkin's lymphoma (HL) is one of the most curable pediatric cancers, however it is rare among children under five years of age and prognostic factors for survival rate are still unknown due to low frequency in this age group.

Objectives. The aim of this study was to evaluate clinical characteristics, treatment regimens, and outcome of patients under five years of age with HL.

Methods. Patients diagnosed with HL between 1972 and 2013 were retrospectively evaluated. All patients were treated with chemotherapy with or without radiotherapy.

Results. There were 102 patients with a median age of 4 years (range: 2 to 4.9). The median follow-up time was 13 years. Twenty-three patients had B symptoms, 15 patients had 'bulky disease' and the most common stages were stage I and II. Overall survival (OS) rates were significantly different according to the stage of the cancer ($p = 0.008$). Although there were no statistically significant differences; the positivity of 'bulky disease' and B symptoms were associated with poor prognosis.

Conclusion. Our single-center study included the largest number of patients under five years of age with HL. The stage was the main predictor for OS; on the other hand, the presence of B symptoms and bulky disease has also affected the prognosis.

Key words: *Hodgkin's lymphoma, adolescent, young adults, child.*

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INTRODUCTION

Hodgkin's lymphoma (HL) mainly occurs in adolescent and young adults, with less prevalence observed among children. In developed countries, the disease is very rare among children under five years of age, therefore the precise causes of HL in early childhood are still unknown.[1] In this age group, poor prognostic factors such as bulky disease, B symptoms, and early stages are less common compared to adolesecent ages. All prior published studies have included limited numbers of patients within this age group.[2,3] There is a recently published study that included one of the larger numbers of patients from Italy that evaluated 135 patients with HL.[4]

The treatment for children with HL generally requires a combination of risk-adapted multi-agent chemotherapy with low-dose involved field radiotherapy (IFRT). This combined therapy aims to reduce the occurrence of therapy-related toxicities, including acute myeloid leukemia, infertility, and cardiotoxicity.[3,5,6] The aim of this study was to evaluate clinical characteristics, treatment regimens, and the outcome of patients under five years of age with HL.

MATERIALS AND METHODS

The patients who were diagnosed and treated with HL under 5 years of age in Hacettepe University, Department of Pediatric Oncology between 1972 and 2013 were enrolled in the study.

The patients were assessed retrospectively based on their epidemiological, clinical,

histopathological characteristics, B symptoms (fever, night sweats and weight loss), extranodal diseases, treatment options, complications, and outcomes. The data was collected with the approval of the Institutional Research Advisory Council.

Diagnosis of HL was made through the histopathological examination of biopsy samples from the patients. Histopathological subtypes were constituted from two main groups: classical and nodular lymphocyte predominant. Classical HL consisted of four subtypes: lymphocyte-rich, mixed cellularity, lymphocyte-depleted, and nodular sclerosis.

The staging was done before the initiation of treatment according to the Ann Arbor staging criteria. Staging work-up included chest X-rays, abdominal ultrasounds, thoracic and abdomino-pelvic computed tomography (abdominal computed tomography includes pelvic imagings; lung computed tomography includes neck component) in addition to physical examinations and laboratory tests. During the period when advanced investigation techniques did not exist, staging was done through physical examinations, bone marrow biopsies, chest X-rays and staging laparotomies. Patients displaying B symptoms were considered having unfavorable diseases.

Chemotherapy protocol

Each patient received chemotherapy and radiotherapy; however, treatment protocols were modified over the years. In the first period, all patients regardless of their stages or histopathology were treated with 6 courses of COPP (cyclophosphamide, vincristine, procarbazine and prednisolone-cyclophosphamide 600 mg/m^2 on days 1 and 7, intravenously, vincristine 1.4 mg/m^2 on days 1 and 7, intravenously, prednisolone 40 mg/m^2 peroral for 14 days, procarbazine 100 mg/m^2 peroral for 14 days) protocol and radiotherapy.

In the second period, stage I and II patients with mixed cellularity (MC) and lymphocyte predominant forms were treated with three courses of COPP with the same doses and involved field 2 250 cGy radiotherapy. Stage I and II patients with nodular sclerosing (NS) or lymphocyte depleted histopathology were treated with three courses of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine-adriamycin 25 mg/m^2 on days 1 and 14, intravenously, bleomycin 10 mg/m^2 on days 1 and 14, intravenously, vinblastine 6 mg/m^2 on days 1 and 14, intravenously, dacarbazine 375 mg/m^2 on days 1 and 14, intravenously) and IFRT. All stage III and IV patients were treated with three courses of COPP and involved field radiotherapy. During the third and fourth period, patients received ABVD chemotherapy and involved field radiotherapy. In those periods, early-stage patients received three courses of chemotherapy; those in advanced stages underwent a six-course sandwich chemotherapy protocol. The doses were as previously described. In the last decade, to decrease infertility risk, boys with mediastinal disease were treated with the ABVD/COPP alternating regimen that also consisted of three courses in early stages and 6 courses in advanced stages.

Radiotherapy protocol

Cobalt 60 teletherapy unit was used until 1993 and linear accelerator with 6 MV x-rays thereafter. Conventional fractionation was used using daily fractions of 150 to 180 cGy. No specific immobilization device was used during treatment. In few patients, vacuumed immobilization beds or thermoplastic immobilisation masks were used. Radiotherapy was applied as mantle, minimantle, and inverted Y according to disease extension in early years. Involved field radiotherapy conforming to the regions of the Ann Arbor classification was used later. Total radiotherapy dose was decided depending on response to the chemotherapy and initial volume of the disease. Total radiotherapy doses in the first period were between 3,000 and 4,000 Gy. Total radiotherapy doses afterwards ranged between 2,000 to 2,500 cGy (Median dose: 2,250 cGy). Sedation was used during radiotherapy when needed.

Multi-agent chemotherapy, combined with low-dose IFRT, has been the main option for the treatment of patients. Patients diagnosed during 1971-1980 received COPP chemotherapy and radiotherapy. Those diagnosed during 1981-1990 as having early stages of disease and either mixed cellularity or lymphocyte predominant histopathological subtypes received a combination of three cycles of COPP and IFRT. The patients in advanced stages during the same period received the combination of three cycles of COPP and three cycles of ABVD with involved field radiotherapy. The patients in the early stages, diagnosed between 1990 and 2000 and beyond, received three cycles of ABVD, whereas those advanced stages received alternating six

cycles of COPP/ABVD along with IFRT. The patients diagnosed in 2010 have received risk-adapted combined therapy. The patients were treated according to response to PET CT after 2010.

The Statistical Package for Social Sciences (SPSS) version 18.0 was used for all statistical analysis. Event-free survival (EFS) was defined as the period from patient enrollment till the date of the first event (relapse, progression, or death from any cause) or till the date of last follow-up. OS was defined as the period from enrollment till the date of death from any cause or till the last follow-up. The trends of both OS and EFS were estimated using the Kaplan-Meier method. The log-rank test was used to compare differences in OS and EFS rates. A p-value less than or equal to 0.05 was considered statistically significant.

The ethical approval was obtained from institutinal review board, and there is no conflict of interest.

RESULTS

One hundred and two patients under five years of age were selected from 728 patients with HL (14 %) and enrolled in the trial (*Figure 1*). Demographic and clinical characteristics of the patients are listed in *Table 1*. The male-female ratio was 3.8:1. The median age was 4 years (range: 2 to 4.9). Forty-seven patients (46 %) were diagnosed between 1981-1990**.** Twenty-five patients (25 %) had stage III-IV disease, while 77 (75 %) had stage I and II disease. Twenty-two patients (22 %) displayed systemic B symptoms.

FIGURE 1. *Flow chart showing the patient selection*

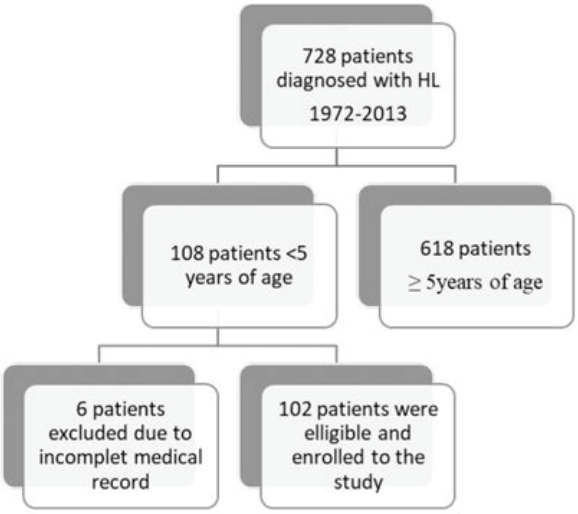

TABLE 1. *Clinical characteristics of 102 patients with Hodgkin lymphoma under 5 years*

	Number of patients	%
Sex		
Male	81	79.4
Female	21	20.6
Diag. period		
1970-1980	12	11.8
1981-1990	47	46.0
1991-2000	29	28.5
>2000	14	13.7
Primary tumor localization		
Cervical	91	89.5
Axilla	5	5.2
Abdomen	4	3.5
Mediasten	2	1.8
''Bulky'' disease		
Present	15	14.7
Absent	87	85.3
Extranodal disease		
Present	7	6.9
Absent	95	93.1
B symptoms		
Present	23	22.5
Absent	79	77.5
Sedimentation rate		
High	31	30.4
Low	19	18.5
Unknown	52	50.1
LDH		
High	31	30.4
Low	23	22.5
Unknown	48	47.1
Leukocytosis		
Present	33	32.4
Absent	69	67.6
Anemia		
Present	24	23.5
Absent	78	76.5
Stage		
I	45	44.1
II	32	31.4
III	16	15.7
IV	9	8.8
Histopathological type		
Mixed cellularity	63	62.2
Lymphocyte rich	11	11.1
Nodular sclerosis	12	11.4
Lymphocite deplated	3	2.2
Nodular lymphocite predominant	2	2.0
Unclassified	11	11.1
Chemotherapy		
COPP	59	57.7
ABVD	19	18.7
ABVD-COPP	14	13.9
MOPP	3	2.9
Not received	7	6.8

LDH: Lactate dehydrogenase; COPP: cyclophosphamide, vincristin, procarbazine and prednizone; ABVD: doxorubisin, bleomycin, vinblastine and dacarbazine; ABVD-COPP: doxorubisin, bleomycin, vinblastine and dacarbazine-cyclophosphamide, vincristin, procarbazine and prednizone; MOPP: mechlorethamine hydrochloride, vincristine sulfate (oncovin), procarbazine hydrochloride, prednizone.

Fourteen patients (14 %) had ''bulky disease''. The disease was mainly localized in cervical lymph nodes, as observed in 96 patients.

The most common subtype was mixed cellularity with 63 patients, while the other subtypes were nodular sclerosis, lymphocytic predominance, lymphocytic depletion, nodular lymphocyte predominant, and unclassified with 12, 11, 3, 2, and 11 patients, respectively. Fifty-nine (58 %) received COPP, 19 (19 %) received ABVD, 14 patients (14 %) received alternated ABVD-COPP, three patients (3 %) received MOPP (mechlorethamine hydrochloride, oncovin, procarbazine hydrochloride, prednisolone) chemotherapy and seven patients (6 %) did not receive any chemotherapy. Eighty-eight patients received involved field radiotherapy. We had two patients that had secondary thyroid carcinoma within the radiotherapy field.

The rates of OS and EFS rates were 89.7 %

FIGURE 2. *Rates of overall survival and event-free survival*

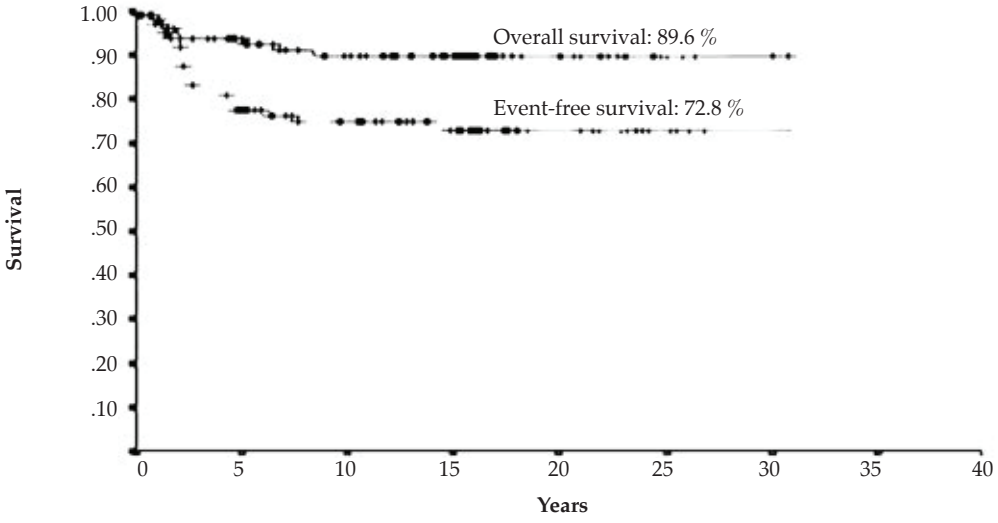

TABLE 2. *Event-free and overall survival rates according to stage, chemotherapy, years, B symptoms and blood parameters*

		EFS	p	OS	p
SR	High	82.3	**0.005**	96.8	
	Normal	94.7		100	**0.037**
Anemia	Positive	64.7	0.245	76.5	**0.023**
	Negative	76.6		94.5	
Period of years	1970-1980	45.8	**0.01**	81.8	0.430
	1980-1990	65.9		86.8	
	1990-2000	86.2		92.9	
	2000-2013	90.9		100	
B symptoms	Positive	53.3	**0.018**	77.8	0.071
	Negative	78		92.9	
LDH	High	41.1	**0.009**	93.3	0.129
	Normal	93.8		100	
Stage	I	68.1	**0.051**	95.1	0.540
	II	79.2		85.9	
	III	68.1		84.4	
	IV	37.5		83.3	
Chemotherapy	None	42.8	**0.02**	71.4	0.22
	COPP	68.5		88	
	ABVD	93.7		100	
	ABVD-COPP	82.5		92.8	
	MOPP	50		100	

SR: sedimentation rate; LDH: lactate dehydrogenose; EFS: event-free survival; OS: overall survival.

and 74.8 %, respectively (*Figure 2*). The median follow-up time was 13 years. The rate of OS was 97.0 % in the patients with stage Ia disease, while it was 75 % in patients with stage IVa disease. The rates of OS varied significantly with the stage of disease (p= 0.008). The rates of OS in patients with lower hemoglobin levels (under 10 g/dl) was 76 %, while it was 94 % in patients with normal hemoglobin levels (p= 0.023) (*Table 2*). The other significant prognostic factor was sedimentation rate (p= 0.037). Although not statistically significant; the presence of "bulky disease'' and B symptoms were associated with poor prognosis. OS rates were 77 % and 91.9 % in patients with and without ''bulky disease'', respectively (p= 0.09), while they were 77.9 % and 92.9 % in patients with and without B symptoms (p= 0.07).

The prognostic factors affecting the rates of the EFS, were B symptom positivity (p= 0.018), high sedimentation rate (p= 0.005), high LDH levels (p= 0.009), and stage IV disease (p= 0.05).

It is also observed that chemotherapy protocols were affecting the event-free survival rates. ABVD based protocols had a significantly positive effect on event free survival (p= 0.02).

Years period have effect on event-free survival; EFS was 90 % during the last decade, while it was 45 % between the 1970 and 1980 period (p= 0.01). OS has gradually increased over the years (from 81 % during the first period to 100 % during the last decade), although the increase was not statistically significant (p= 0.4).

In multivariate analysis, B symptom positivity (p= 0.006) and years period (p= 0.022) were observed to significantly affect the prognosis.

We did not see any immunodeficiency in this age group.

DISCUSSION

Our study is one of the most comprehensive single center studies in a developing country to evaluate the clinical characteristics and outcomes of HL in patients under five years of age. This is a retrospective study that spans over three decades, although diagnostic tools and treatment strategies have changed during this period.

Hodgkin's lymphoma occurs with less frequency during childhood and the disease is very rare among children under five years of age. The incidence rate of 14 % observed in our study is consistent with other previously published studies.[2,3,6,7] The incidence of HL in patients under five years of age was observed to gradually decrease over the period of our study. As documented in our previous report, between 1971 and 1980, 10 % of the patients were under five years old, between 1981 and 1990 period the incidence was 18 %, and after the year 2000 it was 5 %.[7] This change could be attributed to improvement of the socioeconomical status of our country.[2,3,7,8]

In previously published studies from our country male-female ratio ranged from 2.25 to 3. In other studies that have ben done in developed countries, this ratio ranged from 0.7 to 1.6. In our study, the male-female ratio was 3.8:1 which was higher than the ratios documented before.[2,7,9] The disease was most commonly localized in cervical lymph nodes (89.5 %), which was similar to other published studies.[3.8.10,11] Anemia, high level of lactate dehydrogenase, sedimentation rate, and increased white blood cell count correlated with lower survival rates, which was consistent with other studies published.[9,11] Twenty-two patients (22 %) displayed systemic B symptoms and the OS rates were observed to be significantly lower in such patients (p= 0.01). Previously published studies, reported a higher incidence of B symptoms, which was associated with lower survival rates accross all age groups.[2,9,11] Bulky disease was present in 15 of the 102 patients (14.7 %) in our study, which was slightly lower than reported in previously published studies across in all age groups. The presence of bulky disease correlated with lower survival rates.[7,12-14] Bulky disease is one of the worst prognostic factors in patients with Hodgkin lymphoma.

The most common histopathological subtype among our patients was mixed cellularity (62.3 %). The survival rates did not significantly vary with the histopathological subtype. This finding was comparable with other studies done in our country, on patients in both early and late childhood.[2,5] In developed countries, nodular sclerosis was the predominant histopathological subtype, whereas in developing countries mixed cellularity was still the most common subtype across age groups.[13-17] As reported in previously published studies, no statistically significant correlation between the survival rates and histopathological subtypes were found.[11,17,18] The predominance of mixed cellularity in early childhood, as observed in developing countries including ours, could be linked with the early exposure to Epstein-Barr virus or with other carcinogenic factors. We had two patients with nodular lymphocyte predominant histopathology. They were treated with chemotehrapy and radiotherapy. However, for the last 5 years,

treatment options according to the stage were: observation without any treatment, rituximab alone or rituximab combined with chemotherapy respectively.

Twenty-five patients had stage III-IV disease, while 77 had stage I and II disease. The incidence of advanced stages was observed to be lower, which was consistent with other studies carried out on similar age groups. Although the stage of disease did not significantly affect the OS, the rates of OS were higher in early stages of the disease. Event-free survival rates were higher in early stages (p= 0.05). The previously published studies from our country reported early stages to have higher incidence and survival rates than advanced stages among children with HL.[7,9,12] In contrast with our study, one study from our country reported a higher incidence of advanced stages among children under six years of age.[2]

Our general strategy to treat patients has been the use of a combination of two to four cycles of chemotherapy with low dose radiotherapy in early stages and the combination of four to six cyles of chemotherapy with radiotherapy in advanced stages. We had two patients with secondary thyroid carcinoma within the radiotherapy field.

This retrospective study spans three decades of research at our center. The median follow-up time of 13 years is one of the longest periods reported in the literature. The OS and EFS rates were 89.7 % and 74.8 %, respectively. A previous study conducted by Stoneham et al.,[3] on children under 5 years of age, reported the rate of OS for stages II-IV as 89 %, and emphasized that the advanced stages at presentation were the only predictors for prognosis. Belgaumi et al.,[6] reported OS rate of 90.4 % over a 10 years period in children under 5 years of age. EFS rate of 74.8 % was comparable with other studies that were previously published. Stoneham et al. reported EFS rates of 88 % and 68 % from two trials conducted during different time periods, while Belgaumi et al. reported EFS rate of 81.5 % for children under 5 years of age.[3,7,8,14,19] Moreover, in a recent study by Farrugia et al, though the EFS rate was lower than the present study, OS rate (97 %) at 10 years for patients under seven years of age was remarkably higher than the present study.[4]

Univariate analysis of the data indicated that high sedimentation rates and the presence of anemia were linked to decreased OS rates.

In summary, this study is one of the most comprehensive single center studies in a developing country that spans over three decades to evaluate the clinical characteristics and outcomes of HL in patients under five years of age. Although the diagnostic tools and treatment strategies have changed over this long period of time, our findings indicated that the stage of disease and B symptoms were the only predictors for rates of OS and EFS. The trends in these rates were similar to those reported in other studies conducted on patients younger than 5 years and 18 years of age. It is worth consideration by oncologists that this age group has a longer time of remaining life than other age groups. Therefore, the treatment strategy should aim at maintaining the superior OS rates while minimizing the treatment related toxicity for children under 5 years of age. The patients with poor prognostic factors should be treated with different strategies. ■

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