Original Article

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Survival and prognostic factors in childhood Hodgkin's disease; a single centre experience

Childhood Hodgkin's disease survival and prognostic factors; a single centre experience

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Summary

Aim: The aim of this study was to analyze the response and survival rate of pediatric Hodgkin's disease and investigate the parameters influencing the survival.

Material and Method: Forty-three Hodgkin's disease (HD) patients who were treated in our Pediatric Hematology-Oncology Department between 1996 - 2011 were retrospectively analyzed. Twenty-three male and 20 female patients who were younger than 18 year old, newly diagnosed and untreated were included in the study.

Results: The median age was 9 years 5 months, one patient had stage I, twenty-one patients had stage II, twelve patients had stage III and nine patients had stage IV disease. Nineteen patients were in early disease stage and twenty four patients were in advanced disease stage. The most common histological subtype was nodular sclerosis (22 patients). Eighteen of the patients had B symptoms. Hemoglobin levels, leukocyte count, erythrocyte sedimentation rates, serum copper, fibrinogen, lactic dehydrogenase, ferritin and haptoglobin levels were analyzed for response to treatment.

Thirty-eight patients are alive, seven patients relapsed and five patients died. The median follow-up period was 7 years 4 months. The mean overall survival was 12.66 + 0.70 years. The 5-year overall survival was 85.99%. The mean overall survival was 13.10 + 0.81 years for early stages and 12.56+ 0.96 years for late stages.

Conclusions: Bulky disease was bad prognostic factor for OS. Female sex, bulky disease and nodular sclerosis histological subtype were adverse prognostic factors for disease free survival. *(Turk Arch Ped 2013; 48: 310-314)*

Key words: Hodgkin's disease, prognosis, nodular sclerosis

Introduction

Hodgkin's disease is a treatable disease and almost all patients receive chemotherapy as a part of their treatment. The success of treatment is mostly related with prognostic factors. Prognostic factors have been investigated in many studies and tumor burden, stage, bulky disease, B findings, hemoglobin, serum albumin and association of Ebstein Barr virus have been shown as prognostic factors.

The aim of this study was to investigate the variables which influence survival by examining survival times and reponse to treatment in pediatric patients with Hodgkin's disease. With this objective demographic, clinical, laboratory variables and histopathological data were examined.

Material and Methods

A retrospective study was performed with 43 pediatric patients who were followed up and treated in Istanbul Medeniyet University, Göztepe Education and Research Hospital Pediatric Hematology-Oncology clinic between 1996 and 2011.

Grading was done by history, examination findigs, brain, chest and abdominal tomography, gallium scintigraphy and bone marrow biopsy and positron emission tomography

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(PET/CT) in patients with advanced stage and B symptoms. The laboratory tests performed included complete blood count, erythrocyte sedimentation rate, lactic dehydrogenase (LDH), hepatic and renal function tests, serum copper, ferritin, haptoglobin and fibrinogen levels.

Staging was done according to the Ann Arbor staging system. The stages were classified as early and advanced stages. Stage I and IIA were considered as early stages and IIB was considered as the low-risk stage. Stage II and IV were considered as advanced stages and stage IIB was considered as the high-risk stage.

For chemotherapy ABVD (Adriamycin, Bleomycin, Vinblastine, Deticene) was used in 32 patients, ABVD + COPP (Cyclophosphamid, Vincristine, Procarbazine, Prednisone) was used in 3 patients, OPPA (Vincristine, Prednisone, Procarbazine, Adriamycin) + COPP was used in 2 patients, COPP+ABV was used in 3 patients and ARA-C/VP–16 + COPP/ABV + CHOP (Cyclophosphamid, Adriamycin, Vincristine, Prednisone) was used in 1 patient. All patients received "involved field" radiotherapy except for 2 patients.

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, frequency) ch-square test and Fisher's Exact chi-square test were used in comparison of the data. The general survival was evaluated by Kaplan Meier survival analysis and survival according to stages was evaluated by Log Rank (Mantel-Cox) test. A p value of <0,05 was considered significant.

Results

23 of the patients were male (53,4%) and 20 were female (46,6%). The median age was 9 years 5 months (1 year 10 months-17 years 7 months). The distirbution of the disease by regions: 37 neck, 16 abdomen, 21 mediastinum, 1 inguinal and 4 supraclavicular region.

One patient (2,3%) had stage I, 21 (48,8%) patients had stage II, 12 patients (27,9%) had stage III and 9 patients (20,9%) had stage IV disease. 19 patients had early stage and 24 patients had advanced stage disease.

18 patients (41,9%) had B symptoms. The most common histological subtype was nodular sclerosis type which was observed in 22 patients (51,2%). Mixed cell type was observed in 15 patient (34,9%), lymphocyte-rich type was observed in 4 patients (9,3%) and lymphocyte-poor type was observed in 2 patients (4,6%).

The median hemoglobin level was found to be 10,9 g/dL (3,3–13,9). 35 patients had anemia (81,3%). The median leucocyte count was found to be 8,5x109/L (1,8–19,6). 16 patients had leukocytosis (37,2%). Erythrocyte sedimentation rate was measured in 33 patients. The median ERS was found to be 55 mm/h (3-136 mm/h). Serum copper levels were measured in 32 patients. The median copper level was found to be 137µg/dL (53–273 µg/dL). Fibrinogen level was measured in 33 patients. Fibrinogen level was found to be high in 18 patients (54,5). The median fibrinogen level was found to be 432 mg/dL (73-890). LDH level was measured in 38 patients. The median LDH level was found to be 395 IU/L (157–1105). Ferritin levels were measured in 38 patients. The median ferritin level was found to be 86 mg/dL (12,9->5000). Serum haptoglobin levels were measured in 34 patients. The median haptaglobin level was found to be 182 g/dL (1,2–658). Galium scintigraphy was performed in 13 patients and all 13 were found to be positive.

32 patients received ABVD protocol, 3 patients received ABVD + COPP, 2 patients received OPPA + COPP, 2 patients received ABV + OPPA + COPP, 1 patient received ARA-C/VP–16 + COPP/ABV + CHOP protocol. All patients received "involved field" radiotherapy except for 2 patients. The characteristics of the patients are shown in Table 1.

8 patients had recurrence (15,2%). Recurrence was nodal in 5 of these patients, extranodal in one and both nodal and extranodal in one. 2 of these patients were male and 5 were female. The histologic type was nodular sclerosis in 6 patients and mixed cellular type in one patient. One patient had stage IIA, 2 patients had stage IIB, 2 patients had stage IIIA and 2 patients had stage IVB disease. The characteristics of these patients and therapies administered are shown in Table 2.

38 (88,4%) of a total of 43 patients survived, while 5 died. The mean survival time was 12,66 ± 0,70 years. The last exitus was observed in the 5th year; the cumulative survival rate in this month was 85,8% and standard error was 6,1% (Figure 1).

In early stages, the mean survival time is 13,10 ± 0,81 years. In advanced stages, the mean survial time is 12,56+0,96 years. The cumulative survival is 87,8% in early stages and 86,9% in advanced stages (Figure 2). No statistically significant difference was found between the early and advanced stages in terms of mean survival time (p=0,279).

Bulky disease was a negative factor in terms of recurrence and survival time (p<0.05). Gender, early and advanced stages, age group, hemoglobin level, erythrocyte sedimentation rate, leukocyte number, copper, fibrinogen, LDH level, ferritin, haptaglobin, histological subtype and B symptoms did not show statistically significant difference in terms of recurrence and survival time.

For disease-free survival female gender, bulky disease and nodular sclerosis histological subtype were found to be negative prognostic factors, while early or advanced stage, age, ERS, B symptoms, anemia, leukocytosis, copper, fibrinogen, LDH level, ferritin and haptoglobin did not show an influence.

Discussion

23 (53,5%) of our patients were male and 20 were female (46,5%). The male/female ratio was found to be 1,15. The

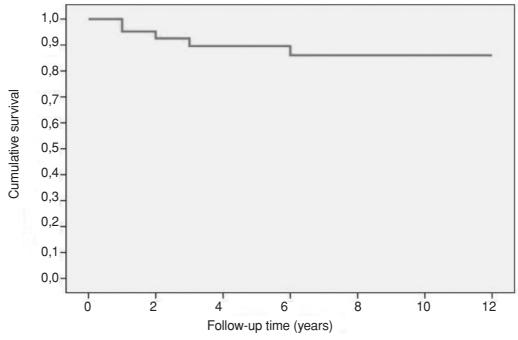
Table 1: Characteristics of the patients

Number of patients	43
Male	23 (53,5 %)
Female	20 (46,5 %)
M/F	1,15
Median age	9 years 5 months (1 year 10 months- 17 years 7 months)
Localization of disease	
Brain	37
Abdomen	16
Mediastinal	21
Inguinal	1
Supraclavicular	4
Stages (Ann Arbor)	
Stage I	1 (2,3 %)
Stage II	21 (48,8 %)
Stage III	12 (27,9 %)
Stage IV	9 (20,9 %)
Type of disease (stage)	
Early stage	19 (44,2 %)
Advanced stage	24 (55,8 %)
B symptoms	
Present	18 (41,9 %)
Absent	25 (58,1 %)
Bulky disease	
Present	11 (25,6 %)
Absent	32 (74,4 %)
Histology	
Nodular sclerosis	22 (51,2 %)
Mixed cell	15 (34,9 %)
Lymphocyte-rich	4 (9,3 %)
Lymphocyte-poor	2 (4,6 %)
Laboratory	
Hemoglobin	3.3 – 13,9 g/dL (median 10.9)
Leukocyte count	1,8 – 19,6 x 109/L (median 8.5)
Erythrocyte sedimentation rate (33 patients)	3 – 136 mm/h (median 55)
Copper (33 patients)	53 – 273 µg/dL (median 137)
Fibrinogen (33 patients)	73 – 890 mg/dL (median 432)
Lactic dehydrogenase (38 patients)	157 – 1105 IU/L (median 395)
Ferritin (38 patients)	12.9 - >5000 mg/dL (median 86)
Haptoglobin (34 patients)	1,2 – 658 g/dL (median 182)
Chemotherapy protocol	
ABVD	32
ABVD+COPP	3
OPPA+COPP	2
ABV+OPPA+COPP	2
COPP/ABV	3
ARA-C/VP16+COPP/ABV/CHOP	1
Radiotherapy	
Involved field radiotherapy	41

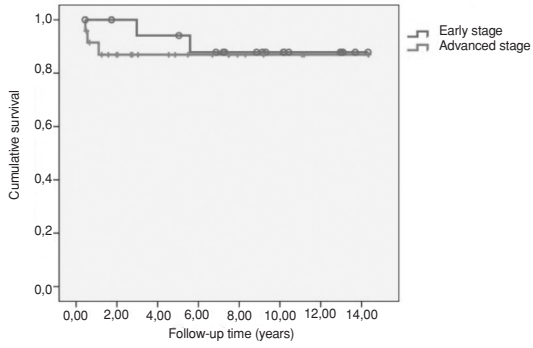
Table 2: Characteristics of the patients who had recurrence and therapies administered

Name	Gender	Histology	Stage	Initial chemotherapy	Recurrence chemotherapy	BMT	Outcome
MY	F	NS	2A	6 ABVD	4 IEP		Died
OO	M	NS	3A	6 ABVD	3 DHAP	Autologous + Allogenic	Surviving
SD	M	NS	2B	6 ABVD	2IEP+2ICE	Autologous	Surviving
SD	F	M	4B	6 ABVD	1 IEP		Died
OC	F	NS	3A	6 ABVD	2 IEP+ABVD+COPP		Surviving
FO	F	NS	4B	6 ABVD	3 ICE	Autologous	Surviving
PA	F	NS	2B	6 ABVD	5 ICE	Autologous	Surviving

F: Female, M: Male, NS: Nodular sclerosis, M: Mixed cell, BMT: Bone marrow transplantation



Şekil 1. Survival documentation



Şekil 2. Survival documentation by early and advanced stages

male/female ratio in patients with Hodgkin's disease varies by age. There is a strong male predominance in children below the age of 5 (M/F=5,3). In children below the age of 15 years the M/F ratio is 1,3 and there is a mild female predominance between the ages of15 and 19 years (M/F=0,8) (1). These ratios in our patients were 1, 1,4 and 1 in our patients, respectively. These rates were compatible with the literature for children below the age of 15 years and between 15 years and 19 years. However, the male/female ratio was equal in patients below the age of 5 which was different from the literature.

6 of our patient (18%) were below the age of 5 years. Hodgkin's disease is observed at an earlier age in developing countries compared to the Western countries. In studies performed in developing countries, 17,6-25% of the cases of Hodgkin's disease have been found to have occured before the age of 5 years (2,3). In developed countries, 3% of the patients with Hodgkin's disease are between the ages of 0 and 4 years (4). Our results are similar to the results of developing countries.

According to the Ann Arbor staging system the distribution of our patients according to stages was as follows: stage 1 2,3%, stage 2 48,8%, stage 3 27,9% and stage 4 9%. Smolewski et al. (5) found the distribution as 8,6%, 33,6%, 42,8% and 15%, respectively. B symptoms are observed in 20-40% of the patients with Hodgkin's disease (6-8). B symptoms were present in 41,9% of our patients. The most common histological subtype in our patients was nodular sclerosis type (51,2%). The most common histological subtype observed in the Western countries is nodular sclerosis type (5,9).

In the study performed by Smolewski et al. (5), it was shown that gender, ESR, leukocyte count or hemoglobin level had no influence on the prognosis of Hodgkin's disease. In our study, ESR, leukocyte count or hemoglobin level had no influence on the prognosis of the disease and female gender was found to be a negative prognostic factor for disease-free survival.

In the study performed by Celkan et al. (10), it was found that hematological values at presentation had no influence on the prognosis in pediatric patients with Hodgkin's disease in contrast to adult patients and no significant difference was found in terms of total survival time by presence of B symptoms or histological subtypes. In our study, hematological variables and presence of B symptoms were not found to be negative prognostic factors

for survival. Nodular sclerosis subtype was found to be a negative prognostic factor in terms of survival.

In the study performed by Garcia et al. (11), pre-treatment serum LDH level was found to be a valuable prognostic factor in pediatric patients with Hodgkin's disease. In our study, LDH level did not show a statistically significant difference between the patients who had recurrence and who did not have recurrence.

In patients with stage IIB Hodgkin's disease, bulky disease was found to be the most important prognostic factor (12). In our study, bulky disease was also found to be an important prognostic factor for disease-free survival and survival in terms of the patients who had recurrence and who did not have recurrence.

In patients with Hodgkin's lymphoma, the 5-year and 10-year survival rates were found to be 96,1% and 94,4% between the years of 1990 and 1994. These reates did not change in the following years. In patients with Hodgkin's lymphoma, the 10-year survival rate was found to be 94,3% between the years of 2005 and 2009 (13). In our study, the 5-year and 10-year survival rate was found to be 85,9%.

In Hodgkin's disease, bulky disease is an important negative prognostic factor in terms of disease-free survival and survival. Female gender, bulky disease and nodular sclerosis subtype is a negative prognostic factor for disease-free survival. Therefore, bulky disease should be treated with more intensive therapy methods and patients with female gender, bulky disease and nodular sclerosis subtype should be monitored more closely. Lactate dehydrogenase level did not gain value as a prognostic factor in our study. This may be related with the number of patients included in our study. A significant portion of our patients were below the age of 5 years which was compatible with the literature. In patients with recurrence, bone marrow transplantation is an efficient treatment method.

Conflict of interest: None declared.

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