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Original Article

Prognostic factors and outcome of ABVD chemotherapy in childhood Hodgkin lymphoma: A single center experience

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Abstract

Aim: The aim was to analyze the outcome of pediatric Hodgkin lymphoma patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy + adjuvant radiotherapy according to the risk groups and determine the adverse prognostic factors affecting survival in Hodgkin lymphoma.

Material and Methods: A retrospective study was performed on 52 pediatric patients with Hodgkin lymphoma who were treated with ABVD between 1997 and 2018. Patients with early-stage favorable disease received 4 cycles of ABVD + radiotherapy. Early-stage unfavorable and advanced-stage patients received 6 cycles of ABVD + radiotherapy.

Results: Thirty (57.7%) boys and 22 (42.3%) girls were included in the study. The median age of the patients was 9 years and 3 months (1 year and 10 month – 17 years and 7 months). Overall survival rate was 94.2% and the mean survival time was 19.5±0.70 (95% CI, 18.1 - 20.9) years. The mean event-free survival time was 9.5±6.5 years. Overall survival rate was 90%, and the mean event-free survival time was 8.2±6.1 years in early-stage favorable disease. Overall survival rate was 100%, and the mean event-free survival time was 1.9±7.0 years in early-stage unfavorable disease. Overall survival rate was 94.1 %, and the mean event-free survival time was 8.9±6.3 years in advanced-stage disease. Presence of bulky disease, nodular sclerosing histologic subtype and leukocytosis had a negative prognostic effect on relapse and bulky disease had adverse effect on overall survival ($p<0.05$).

Conclusion: Four courses of ABVD chemotherapy + radiotherapy (IFRT or ISRT) in early-stage favorable patients and 6 courses of ABVD chemotherapy + radiotherapy (IFRT or ISRT) in both early-stage unfavorable and advanced-stage Hodgkin lymphoma patients benefited from promising outcomes in terms of OS and FFS.

Presence of bulky disease, nodular sclerosing histologic subtype and leukocytosis have adverse prognostic effects on relapse and presence of bulky disease have adverse effect on OS.

Keywords: Hodgkin lymphoma; prognosis; overall survival.

INTRODUCTION

Hodgkin lymphoma is a curable disease, and chemotherapy is an integral part of the treatment in the majority of patients. The standard approach to treatment uses doxorubicin, bleomycin, vinblastine, and dacarbazine regimen as first-line therapy (1). The treatment strategies with ABVD chemotherapy differs in many centers (2-8). In early-stage disease short-course chemotherapy (2–4 cycles) followed by radiotherapy (20–30 Gy) has demonstrated high efficacy and acceptable acute and long-term toxicity, with cure rates that exceed 90% (9). In advanced-stage disease 6-8 cycles of ABVD chemotherapy plus radiotherapy remains the standard care.

In Hodgkin disease the success of treatment depends mainly on prognostic and risk factors which have been investigated in various studies; tumor load, stage of disease, presence of bulky disease, presence of B symptoms, hemoglobin, serum albumin, and coexistence of Epstein-Barr virus were suggested as prognostic factors (10-13). In adults International Prognostic Score (IPS), which incorporates seven clinical parameters, has been the most widely accepted risk stratification model (14). Unfortunately, IPS is not a valid system for children; therefore more randomized studies are required for establishing the risk factors pediatric age group.

In this article we discuss the outcome of pediatric Hodgkin lymphoma patients treated with 4 courses of

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ABVD chemotherapy + radiotherapy (IFRT or ISRT) in early-stage favorable patients, and 6 courses of ABVD chemotherapy + radiotherapy (IFRT or ISRT) in both early-stage unfavorable and advanced-stage patients and validate the adverse prognostic factors affecting survival in Hodgkin lymphoma.

MATERIAL and METHODS

A retrospective study was performed on 52 pediatric patients with Hodgkin lymphoma who were treated with ABVD chemotherapy between 1997 and 2018 in Pediatric Hematology and Oncology Clinic.

Boys and girls aged between 0 and 17-years-11 month old with Hodgkin lymphoma who received ABVD chemotherapy and adjuvant radiotherapy were included in the study. The patients who received chemotherapy other than ABVD protocol or ABVD plus hybrid treatments, 1 patient with nodular lymphocyte dominant histology and who did not receive radiotherapy were excluded from the study. Informed consent was obtained from all patients.

The institutional ethics committee approved the study (2019/0008).

The staging was done by history, physical examination, cervical/thoracic/abdominal Computerized Tomography (CT) or Magnetic Resonance Imaging (MR), or F-18-fluoro-2-deoxyglucose positron emission tomography (FDG/PET). In cases with advanced disease, or patients with B symptoms bone marrow biopsy was performed. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), liver and renal function tests, copper, ferritin, haptoglobin, and fibrinogen in serum levels were studied as laboratory tests. All patients were staged according to the Ann Arbor classification system. Patients were classified as early-stage favorable, early-stage unfavorable or advanced-stage disease. Early-stage favorable patients were defined as low-risk stage I or II (without B symptoms, large mediastinal mass or extranodal involvement, and erythrocyte sedimentation rate <50 mm/h). Early-stage unfavorable patients were defined as high-risk stage I or II (with B symptoms, large mediastinal mass or extranodal involvement, and erythrocyte sedimentation rate >50 mm/h). Patients with the advanced-stage disease were defined as stage III or IV.

Patients with early-stage favorable disease received 4 cycles of ABVD chemotherapy + involved field or involved site radiotherapy. Early-stage unfavorable and advanced-stage patients received 6 cycles of ABVD chemotherapy + involved field or involved site radiotherapy. ABVD chemotherapy includes the drugs Doxorubicin 25 mg/m^2 IV, Bleomycin 10,000 IU/m^2 IV, Vinblastine 6 mg/m^2 IV, Dacarbazine 375 mg/m^2 IV on days 1 and 15 of every cycle.

The data were analyzed on the computer using SPSS 25.0 (Statistical Packages of Social Sciences) program. Descriptive statistics were shown as frequency and percentage for categorical variables.

Distributions of variables were evaluated by Fisher's exact test. Survival was evaluated by using Kaplan–Meier analysis. P value less than 0.05 was considered as statistically significant.

RESULTS

Thirty (57.7%) boys and 22 (42.3%) girls were included in the study. The demographic characteristics are seen in Table 1.

Table 1. Clinical and laboratory characteristics of the patients

All patients	52 (100%)
Gender	
Male	30 (57.7%)
Female	22 (42.3%)
Male/Female	1.36
Median age	9 years 3 months (1 year - 10 months - 17 years 7 months)
Involved regions	
Cervical	47
Abdominal	13
Mediastinal	24
Inguinal	3
Supraclavicular	19
Stages (Ann Arbor)	
Stage I	1 (1.9%)
Stage II	34 (65.4%)
Stage III	5 (9.7%)
Stage IV	12 (23%)
Early-stage favorable	20 (38.5%)
Early-stage unfavorable	15 (28.8%)
Advanced stage	17 (32.7%)
B symptoms	
Present	21 (40.4%)
Absent	31 (59.6%)
Bulky disease	
Present	9 (17.3%)
Absent	43 (82.7%)
Histologic subtypes	
Nodular sclerosing	26 (50%)
Mixed cellularity	18 (34.6%)
Lymphocyte-rich	7 (13.5%)
Lymphocyte depletion	1 (1.9%)
Hemoglobin	7.2 – 13.6 g/dl (median 11)
Leukocyte	4.3 – 19 x 10^9/L (median 8,25)
Sedimentation (31 patients)	5 – 112 mm/hour (median 44)
Copper (46 patients)	27.4 – 273 µg/dl (median 140)
Fibrinogen (41 patients)	147 – 949 mg/dl (median 362)
Lactic dehydrogenase	169 – 1105 IU/L (median 335)
Ferritin (47 patients)	6.89 - 4223 mg/dl (median 54.2)
Haptoglobin (47 patients)	0.87 – 658 g/dl (median 106)

The median age of the patients was 9 years and 3 months (1 year and 10 month – 17 years and 7 months). The involved regions of the disease were as follows; 47 cervical, 24 mediastinal, 13 abdominal, 19 supraclavicular, and 3 inguinal.

There were 1 (1.9%) stage I, 34 (65.4%) stage II, 5 (9.7%) stage III, and 12 (23%) stage IV patients. Twenty (38.5%) patients had early-stage favorable, 15 (28.8%) had early-stage unfavorable, and 17 (32.7%) had advanced-stage diseases.

B symptoms were present in 21 (40.4%) patients. Bulky disease was present in 9 (17.3%) patients. The nodular sclerosing type was the most common histologic subtype which was seen in 26 (50%) patients. Other subtypes were as follows; 18 (34.6%) mixed cellularity, 7 (13.5%) lymphocyte-rich classical Hodgkin lymphoma, 1 (1.9%) lymphocyte depletion types. The laboratory results are seen in Table 1.

All 20 patients with early-stage favorable disease received 4 cycles of ABVD chemotherapy + involved field (IFRT) or involved site (ISRT) radiotherapy. There were 2 patients in this group in whom remission could not be achieved; they received 2 additional cycles of ABVD chemotherapy. Fifteen patients with early-stage unfavorable and 17 patients with advanced-stage disease received 6 cycles of ABVD chemotherapy + involved field or involved site radiotherapy.

Relapse was observed in 8 (15%) patients (2 boys, 6 girls). Relapse was nodal in six, extranodal in one, and one patient had both nodal and extranodal relapses. Histologic type was nodular sclerosing in 7 and mixed cellularity in 1 patient. The distributions of relapsing cases according to stages were as follows: 1 had stage IIA, 2 had stage IIB, 2 had stage IIIA, and 3 had stage IVB diseases. Two of the relapsing patients died. One of the patients who died was stage 2A nodular sclerosing histologic subtype, and the other was stage 4B mixed cellularity subtype. Five of 8 relapsing patients had bone marrow transplantation, and they are all alive. Three of these patients were in advanced-stage, one in early-stage favorable and one in early-stage unfavorable disease. The properties and treatments of relapsing patients are given in Table 2.

Table 2. Characteristics of relapsing patients and treatments

Patient	Gender	Histologic subtype	Stage	Primary chemotherapy	Relapse chemotherapy	ASCT/ alloSCT	Outcome
MY	F	NS	2A	6 ABVD	4 IEP		Dead
OO	M	NS	3A	6 ABVD	3 DHAP	ASCT + alloSCT	Alive
SD	M	NS	2B	6 ABVD	2IEP + 2ICE	ASCT	Alive
SD	F	MC	4B	6 ABVD	1 IEP		Dead
OC	F	NS	3A	6 ABVD	2 IEP + ABVD + COPP		Alive
FO	F	NS	4B	6 ABVD	3 ICE	ASCT	Alive
PA	F	NS	2B	6 ABVD	5 ICE	ASCT	Alive
SB	F	NS	4B	6 ABVD	2 ICE	ASCT	Alive

F: Female, M: Male, NS: Nodular sclerosing, MC: Mixed cellularity, ASCT: Autologous stem cell transplantation, alloSCT: Allogeneic stem cell transplantation, IEP (Ifosfamide, Etoposide, Prednisone), DHAP (Dexamethasone, High-dose Cytarabine, Cisplatin), ICE (Ifosfamide, Carboplatin, Etoposide), COPP (Cyclophosphamide, Vincristine, Procarbazine, Prednisone), ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine)

Out of 52 patients, 49 (94.2%) survived; there were 3 (5.8%) deaths. The cause of death was sepsis in 2 patients. Overall survival rate was 94.2% and the mean survival time was 19.5±0.70 (95% CI, 18.1 - 20.9) years. (Figure 1). The mean event-free survival time was 9.5±6.5 years.

Overall survival rate was 90%, and the mean event-free survival time was 8.2±6.1 years in early-stage favorable disease. Overall survival rate was 100%, and the mean event-free survival time was 11.9 ±7.0 years in early-stage unfavorable disease. Overall survival rate was 94.1%, and the mean event-free survival time was 8.9±6.3 years in advanced-stage disease (Figure 2).

Presence of bulky disease, nodular sclerosing histologic subtype and leukocytosis had a negative prognostic effect on relapse and bulky disease had adverse effect on overall survival (p<0.05).

There was no statistically significant difference in comparison of overall survival rates of early-stage favorable, early-stage unfavorable, and advanced-stage disease patients (p>0.05).

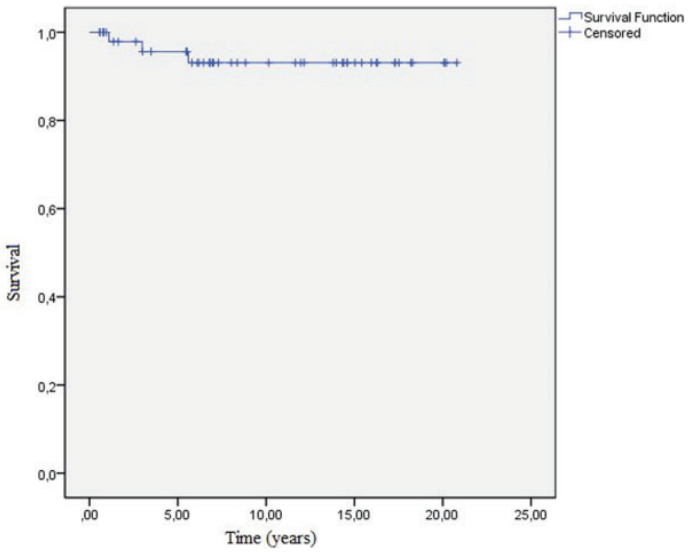

Figure 1. Overall survival

Presence of bulky disease, nodular sclerosing histologic subtype and leukocytosis had an adverse prognostic

effect on relapse and presence of bulky disease had adverse effect on overall survival time (p<0.05). On the other hand, gender, early or advanced-stages, age group, hemoglobin, copper, fibrinogen, LDH, ferritin, and haptoglobin levels, and B symptoms had no statistically significant prognostic effects on relapse (Table 3).

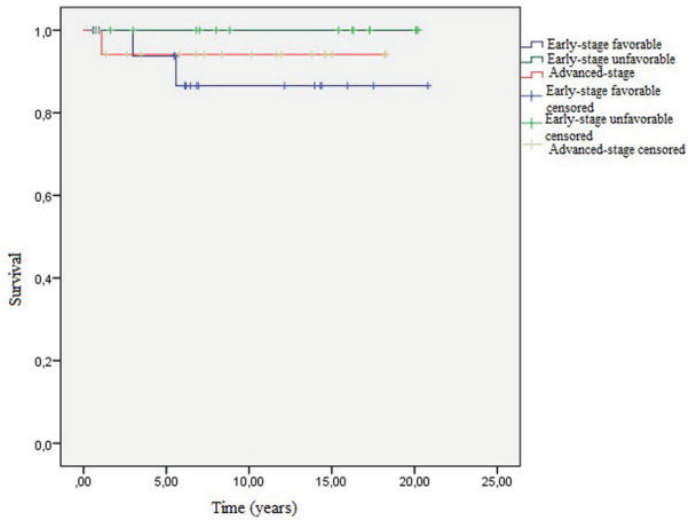

Figure 2. Survival analysis for early-stage diseases and advanced-stage disease

Table 3. Effects of various variables on relapse and survival

	Relapse	Surviv-al
	p	p
Gender	0.058	0.070
Stage	0.225	0.916
Histologic subtypes		
Nodular sclerosing	**0.049***	1.000
Mixed cellularity	0.236	1.000
Lymphocyte-rich	0.578	1.000
Lymphocyte depletion	1.000	1.000
Early stage/Advanced stage	0.118	0.454
A/B	0.314	0,937
Bulky disease	**0.004***	**0.005***
Anemia	1.000	0.564
Leukocyte	**0.043***	0.551
Sedimentation	0.324	1.000
Copper	1.000	1.000
Fibrinogen	0.093	1.000
Alkaline phosphatase	0.298	1.000
Lactic dehydrogenase	1.000	0.546
Ferritin	0.653	1.000
Haptoglobin	1.000	0.441
<10 years vs >11 years	0.700	1.000

*P value less than 0.05 was considered as statistically significant

DISCUSSION

In Hodgkin lymphoma, there is a strong male preponderance in patients under 5 years of age (M/F=5.3), but this ratio decreases to 1.3 in children under 15 years of age. Between the ages 15-19 years, M/F ratio reverses to 0.8, with a slight female dominance (15). In our series, these ratios were 1.7, 1.9, and 0.3 respectively. Our results were consistent with the literature in patients under 15 years of age and in patients between the ages of 15 and 19 years but were different in patients under 5 years of age. This may be due to small numbers of patients under 5 years old, or the level of low socioeconomic status.

In developing countries, Hodgkin lymphoma occurs more commonly in younger ages than the developed countries. In some studies from developing countries, it was found that 17.6 to 25% of Hodgkin disease patients were under the age of 5 years (16,17). However, in developed countries, only 3% of patients were between 0 to 4 years of age (18). Our results compare favorably to the results of the developing countries. The earlier age suggests that the biology of Hodgkin lymphoma in developing countries is different from that in Western countries (17). The lower socioeconomic level may be another reason for occurrence in early age. In Hodgkin lymphoma, there is no difference in terms of outcome between older children and in children under five years of age. According to Smolewski et al. the distribution of stages was as follows; stage I 8.6%, stage II 33.6%, stage III 42.8% and stage IV 15% (10). Conversely, in our study, the count of patients with stage I disease was very low, and the count of stage III and stage IV patients was high. In the developing countries, the delay in hospital admission due to socio-economic reasons leads to the diagnosis of their disease when it has reached an advanced stage. B symptoms occur in 20-40% of Hodgkin disease patients (19-21). This is similar to our results.

The most common histopathological subtype in our patients was nodular sclerosing type (50%). This type is also the most common one in western countries (10,22,23).

A study from Turkey suggested that unlike the adults, in pediatric Hodgkin lymphoma patients the hematological values obtained during the patient admission have no influence on the course of the disease, the presence of B symptoms, or histopathological subgroups have no significant differences in overall survival rates (4). Our study also revealed similar results except for leukocyte count. In our study, the presence of leukocyte count had an adverse prognostic effect on relapse and survival.

Various studies reported bulky disease, B symptoms, total leukocyte count, lymphopenia and LDH as an adverse prognostic factor (12,13,24). In this study leukocytosis, nodular sclerosing histologic subtype and bulky disease are adverse prognostic factors for overall survival and disease-free survival of relapsed and non-relapsed patients. In this study B symptoms, lymphopenia and LDH did not affect the outcome.

Five and 10-year survival rates of Hodgkin Lymphoma patients between the years 1990 and 1994 were reported as 96.1% and 94.4%, respectively. These rates did not alter in subsequent years. Projected 10-year survival rates for

children diagnosed in the 2005 – 2009 period were 94.3% (25). In our study, 5 and 10-year survival rates were also found as 94.2% and compared favorably with the results.

In a study carried out by Meyer et al. a very well prognosis was reported in early-stage Hodgkin Lymphoma patients, and depending on additional risk factors the long term remission rates reached up to 90 to 95% (26). The survival rate in our study was 90% in early-stage favorable disease. In cases of the early-stage unfavorable disease, the overall survival rate was 100%. In early-stage unfavorable disease, 6 cycles of ABVD chemotherapy may be considered as an effective treatment.

Engert et al. reported FFS as 83% and general survival rate as 91% in advanced-stage patients who received 6 cycles of ABVD therapy (26). In the present study, these ratios were 94.2% and 94.1% respectively in advanced-stage disease patients, depicting slightly better results.

The standard treatment for relapsed and primary refractory HL is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), which has shown a 5-year progression-free survival rate of ~50%–60% (27,28). Five of our 8 relapsing patients had bone marrow transplantation. All patients are alive. This ratio can be attributed to the small number of patients who underwent ASCT.

The major strength of our study is that all the patients had standard chemotherapy regimen related to risk groups. Although our study is retrospective, all patients with ABVD regimen were included in the study, but there were not an adequate number of patients to identify prognostic factors. Larger patient groups are needed to validate the prognostic factors in pediatric age group.

CONCLUSION

Four courses of ABVD chemotherapy + radiotherapy (IFRT or ISRT) in early-stage favorable patients and 6 courses of ABVD chemotherapy + radiotherapy (IFRT or ISRT) in both early-stage unfavorable and advanced-stage Hodgkin lymphoma patients benefited from promising outcomes in terms of OS and FFS. Salvage chemotherapy followed by ASCT seems like an effective means of treatment in relapsing patients.

Presence of bulky disease, nodular sclerosing histologic subtype and leukocytosis have adverse prognostic effects on relapse and presence of bulky disease have adverse effect on OS. Hodgkin lymphoma. Hodgkin lymphoma patients with bulky disease, nodular sclerosing histologic subtype and leukocytosis are recommended to be followed up closely, and more aggressive treatment protocols may be considered in patients with bulky disease.

In adults IPS is an accepted risk stratification model but is not a valid system for children; therefore more randomized studies with larger number of patients are required for defining the risk factors of pediatric age group.

Competing interests: The authors declare that they have no competing interest.
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