RESEARCH ARTICLE

Efficacy and Safety of First Line Vincristine with Doxorubicin, Bleomycin and Dacarbazine (ABOD) for Hodgkin's Lymphoma: a Single Institute Experience

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Abstract

Background: ABVD (doxorubicin, bleomycin, vinblastine (Vb) and dacarbazine) is the standard regimen in Hodgkin's lymphoma (HL).Vincristine (O) is a mitotic spindle agent like Vb. We aimed to evaluate the efficacy and safety of O as a part of ABOD in HL. Materials and Methods: Patients who had ABOD were enrolled. Stage I-II HL were evaluated for unfavorable risk factors according to NCCN. National Cancer Institute Common Toxicity Criteria was used for toxicity. Results: Seventy-nine HL patients in our center between 2003 and 2007 were evaluated retrospectively. Median follow-up was 54 months. Most of the patients were male in their third decade. Median ABOD cycles were 6 (2-8). Primary refractory disease rate was 17.7% whereas it was 5.1% for early relapse and 5.1% for late relapse disease. Response rates were as 82.3% for complete response, 11.4% for partial response, 5.1% for stable disease and 1.3% for progressive disease. Half of relapsed patients had autologous stem cell transplantation. Estimated 5-year failure-free survival was 71% and significantly longer in early stage patients without risk factors, bulky disease or radiotherapy (RT) (p=0.05, p<0.0001, p=0.02; respectively). Estimated 5-year overall survival was 74% and significantly longer in those who had no RT (p=0.001). Dose modification rate was 5.1% and chemotherapy delay rate was 19%. There were no toxicity-related deaths. Conclusions: ABOD seems to be effective with managable toxicity in HL, even in those with poor prognostic factors.

Keywords: Hodgkin's lymphoma - chemotherapy - vincristine - prognostic factors

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Introduction

The main treatment of Hodgkin lymphoma consists of ABVD (doxorubicin, bleomycin, vinblastine (Vb) and dacarbazine) regimen and/or involved field radiotherapy (IFRT) (Canellos et al., 1992). The number of chemotherapy cycles mainly depends on stage and unfavorable risk factors in early stage (Chakrabarti et al., 2010). The ABVD regimen has become the standard chemotherapy regimen in Hodgkin Lymphoma (HL) after it was shown that ABVD seemed to better than MOPP (mechlorethamine, vincristine, procarbazine and prednisone) and equivalent to MOPP/ABVD with less toxicity (Bonadonna et al., 1975; Canellos et al., 1992). The BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen is another investigated one in advanced stage HL. Viviani et al reported better initial tumor control with BEACOPP in advanced stage, but it had similar long-term outcomes with ABVD (Viviani et al., 2011). Vincristine (O) is a vinca alkaloid which depolymerizes microtubules leading mitotic arrest, like Vb. It has been used as a part of alternating regimen of PABIOE (doxorubicin, bleomycin, vincristine, etoposide) with ChlVPP (chlorambucil, vinblastine, procarbazine, prednisone) besides MOPP and BEACOPP in HL (Cullen et al., 1994; Hancock et al., 2001). However, it is not a standard component of ABVD. We had to use vincristine instead of Vb with doxorubicin, bleomycin and dacarbazine (ABOD) in HL since we could not provide Vb in those years, taking into account our experience with vincristine in MOPP and BEACOPP regimens in HL (Bonadonna et al., 1975; Engert et al., 2009; Fatima et al., 2011). In this study, we aimed to evaluate the efficacy and safety of vincristine as a part of ABOD in HL.

Materials and Methods

We enrolled only classic Hodgkin lymphoma patients

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who had ABOD to the study. Risk classification in the patients with early stage (stage I-II HL) was performed according to National Cancer Comprehensive Network (NCCN). The patients were stratified as early stage with unfavorable risk factors, early stage without unfavorable risk factors and advanced stage. Bulky disease was defined as large mediastinal lymphadenopathy greater than one third of the thoracic diameter at T5 or T6 vertebrae or mass more than 5-10 cm in width. The patients were evaluated for clinicopathological characteristics, response rates, failure-free survival and overall survival (OS) besides chemotherapy efficacy and toxicity. National Cancer Institute (NCI) Common Toxicity Criteria was used for toxicity. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 was used for response evaluation. The patients with no response to the primary treatment were accepted as primary refractory patients. Relapse in the first six months of remission was defined as early relapse whereas relapse after six months was defined as late relapse. The intervals between the date of diagnosis and the date of progression from partial remission or the date of relapse from a complete remission were defined as failure-free survival (FFS) while the interval between the date of diagnosis and the date of death or last known alive was defined as overall survival (OS). Both of regression and stabilization of the disease were defined as clinical benefit.

Statistics

Statistical analyses was performed by using SPSS for Windows version 18.0 (SPSS, Chicago, IL). Tumors with missing values were omitted from the analyses. The data were retrospectively analyzed for FFS and OS according to the risk groups. Kaplan-Meier survival analysis was carried out for FFS and OS. The log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided P values of <0.05 were considered statistically significant.

Results

Seventy nine HL patients admitted to Medical Oncology Department of Ankara Numune Training and Reseach Hospital between December 2003 and November 2007 were evaluated retrospectively. Median follow-up was 54 months. Most of the patients were male in the third decade. Half of the patients (54.5%) had nodular sclerosing-HL. Seventy six percent of the patients had either unfavorable early stage or advanced stage disease. Most (60%) of the patients had B symptoms. The most common B symptoms was weight loss (51%). Bulky disease occured in 27% of the patients at diagnosis.

Treatment efficacy

Median ABOD cycle was 6 (range: 2-8).Response rates were as 82.3% for complete response (CR), 11.4% for partial response, 5.1% for stable disease and 1.3% for progressive disease. One third of the patients had primary refractory or relapsed disease. Primary refractory disease rate was 17.7% whereas it was 5.1% for early relapse and 5.1% for late relapse. Half of relapsed patients had autologous stem cell transplantation (ASCT). Most common preferred salvage chemotherapy regimen before ASCT was ICE (ifosfamide, carboplatin and etoposide) with a rate of 75%. Sixty percent of the patients had IFRT. Median FFS and OS were not reached, but 5-year FFS was 71% while 5-year OS was 74% (Figures 1,2). Estimated 5-year FFS was significantly longer in those with low risk early stage, bulky disease or radiotherapy

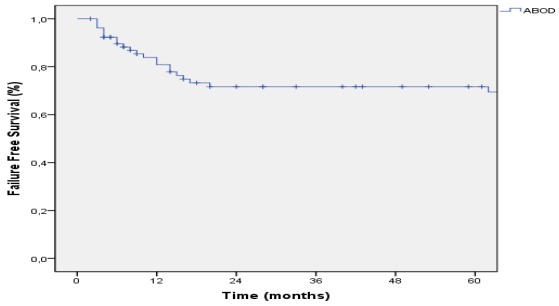

Figure 1. Failure Free Survival (FFS) of the ABOD Group

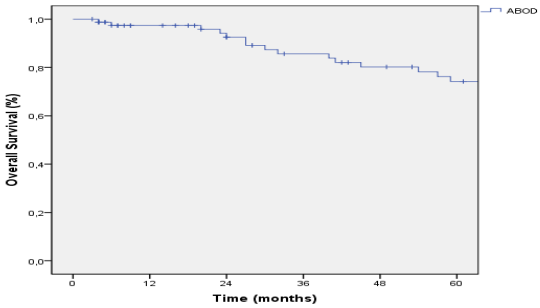

Figure 2. Overall Survival of ABOD Patients

Table 1. The Survival Rates of the Study Population According to the Patient Characteristics

Patient Characteristics		5 yrs FFS (%)	p value	5 yrs OS (%)	p value
Sex	Male	67	0.13	79	0,60
	Female	78		80	
Stage					
Early stage favorable		94		94	
Early stage unfavorable		61	0.05	85	0,07
Advanced stage		64		66	
ECOG-Performance Status (n)					
0-1		74	0.18	76	0,11
2-4		50		50	
Histology					
Nodular sclerosing-HL		66		79	
Mixed cellularity-HL		75	0.86	67	0,36
Lymphocyte rich-HL		72		100	
Lymphocyte depleted-HL		50		100	
LDH	High	65	0.18	84	0,60
	Normal	80		74	
Bulky disease	Yes	42	0.0001	65	0,14
	No	83		86	
Radiotherapy	Yes	82	0.02	94	0,001
	No	54		60	
B symptoms	Yes	68	0.57	76	0,20
	No	75		87	

Table 2. ABOD Related Toxicity Rates

Toxicity	Grade 1-2 n (%)	Grade 3-4 n (%)
Anemia	40 (50.6)	3 (3.8)
Neutropenia	19 (24.1)	10 (12.6)
Thrombocytopenia	3 (3.8)	1 (1.3)
Hepatotoxicity	3 (3.8)	0 (0)
Renal toxicity	6 (7.6)	1 (1.3)
Peripheral neuropaty	8 (10.1)	1 (1.3)
Total	79 (100)	16 (20)

Table 3. Response and Severe Toxicity Rates with Comparison of ABOD and Historical ABVD Control

		ABOD (n=79) %	ABVD (n=115) %
ECOG-PS	0-1	82.3	90
	2	10.1	10
	3-4	7.6	0
Response rates (%)	Complete response	82.3	82
	Partial response	11.4	13
	Stable disease	5.1	2
	Clinical benefit (%)	98.8	97
Severe toxicity rates (%)	Anemia	3.8	5
	Thrombocytopenia	1.3	2
	Neutropenia	12.6	18
	Febrile neutropenia	2.5	2
	Peripheral neuropathy	1.3	1
Total		21.5	28
	5 yea-FFS (%)	71	61
	5 year-OS (%)	74	73

*ECOG: Eastern Cooperative Oncology Group, FFS: Failure-Free Survival, OS: Overall Survival, PS: performance score

(RT) in univariate analysis (p=0.05, p<0.0001, p=0.02; respectively). Estimated 5-year OS was significantly longer in those who had no RT (p=0.001). The early stage HL patients without risk factors had also longer OS, however the difference was not statistical significant (p=0.07). The patient characteristics which might affect survival are listed in Table 1.

Toxicity

The toxicity rates are summarized in Table 2. Grade 3-4 toxicity rates were as 12.6% for neutropenia, 3.8% for anemia, 2.5% for febrile neutropenia and 1.3% for thrombocytopenia or neuropathy or nephrotoxicity. Dose modification was applied to 5.1% of the patients whereas chemotherapy was delayed in 19% of the patients. There was no toxic death.

Discussion

Treatment of HL depends on stage and risk factors. ABVD and/or IFRT are the standard modalities in HL (Canellos et al., 1992; Meyer et al., 2005; Meyer et al., 2012). The Stanford V regimen is also an alternative regimen for early stage without poor prognostic factors while the results of escalated BEACOPP regimen in unfavorable early stage and advanced stage are encouraging (Advani et al., 2013). However, escalated BEACOPP has high toxicity rates such as more than 80% grade 3/4 hematological toxicity and 3% toxic death, even in younger patients (<60 years) with better performance status (Diehl et al., 1998; Viviani et al., 2011).

Vincristine was used as a part of ABOD in our study taking into account the experience with other regimens like MOPP and BEACOPP. We had to use it because of Vb shortness as mentioned before. We preferred to compare our ABOD results with historical ABVD control by Canellos, since it is the standard chemotherapy regimen in HL (Table 2-3) (Canellos et al., 1992). Our patients had male predominance in the third decade like historical ABVD control study (Canellos et al., 1992). The response rates were comparable despite lower rate of patients with better performance status in our study [82.3% *versus* 90% for ECOG-PS (0-1)]. In addition, approximately 8 % of our patients had poor performance status (ECOG-PS: 3-4) though there was no patient with poor PS in historical ABVD control study. The response rates similar in both studies. Five-year OS was also similar whereas 5-year FFS seems to be quite higher in our patients (73% *versus* 74%, 71% *versus* 64%, respectively).

The severe toxicity profile did not differ from ABVD historical control (Table IV). Severe neutropenia was lower (12.6% *versus* 18%) while febrile neutropenia was similar (2.5% *versus* 2%) in comparison of ABOD and ABVD regimens (Canellos et al., 1992). Our patients had more grade 3/4 peripheral neuropathy (1.3% *versus* 1%) although vincristine and Vb are members of the same family. Inspite of similar mechanism of vinca alkaloids, Vb seems to have more intracellular retention than vincristine (Abu-Khalaf MM, 2011). It might lead rarely different toxicity profiles like hematologic side effects. Neutropenia is a dose-limiting side effect with Vb while it is rare with vincristine. We consider that this might have contributed to less neutropenia in our patients. There was no toxic death in our study. However, we consider that our study might have also some limitations while evaluating toxicity profile since it is retrospective.

In conclusion, high clinical benefit with managable toxicity with ABOD regimen seems to be encouraging in HL. We consider that in shortage of vinblastine, vincristine seems to be a reliable substitute for Vb. However, further prospective trials with large number of patients are needed for ABOD in HL.

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