Treatment Outcomes and Toxicities of ABVD Combination Chemotherapy Compared with CVPP in Hodgkin's Disease

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Background: We retrospectively evaluated the treatment outcomes and toxicities of Hodgkin's disease (HD) patients treated by ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) combination chemotherapy, and compared them with those of a historical group treated with a CVPP (cyclophosphamide, vinblastine, procarbazine, and prednisone) regimen.

Methods: The medical records of patients who had been diagnosed with HD histologically and treated by either ABVD or CVPP from 1997 to 2006 at the Korea University Medical Center were retrospectively reviewed.

Results: Thirty patients were eligible. Nineteen patients received ABVD and eleven patients were treated with CVPP. The response rates for ABVD and CVPP were 84.21% and 54.55%, respectively. Median overall survival was 43.17 months for ABVD and 43.27 months for CVPP (*P*=.570). Median event-free survival was 39.03 months for ABVD and 16.73 months for CVPP (*P*=.088). There was no significant difference in median survival or in event-free survival between the two regimens. Hematologic toxicities were significantly more common in the CVPP group than in the ABVD group. Grade 3 or 4 neutropenia was observed in 72.72% of the CVPP group and in 36.84% of the ABVD group (*P*=.050).

Conclusion: ABVD for HD showed significantly lower hematologic toxicities and moderately better treatment outcomes than did CVPP. ***(Korean J Hematol 2007;42:335-342.)***

Key Words: Hodgkin's disease, Chemotherapy, Toxicity

INTRODUCTION

Hodgkin's disease (HD) is known to be sensitive to combination chemotherapy and is considered a curable disease. In 1964, Devita et al. introduced MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy for the treatment of HD[1] and many subsequent reports confirmed its effectiveness.[2,3] None of the modified regimens which followed MOPP were able to demonstrate significant superiority until the ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) regimen was developed in 1974.[4] ABVD was able to cure approximately one fifth of patients who showed no response to MOPP therapy.[5] Though many hybrid regimens (those which alternate administration of MOPP and ABVD) have been recently introduced, trials have failed to

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reveal superior efficacy over ABVD alone.[6-9)]

Korean studies on treatment outcomes for HD have been relatively uncommon due to the lower incidence of HD compared to western countries.[10,11)] Of the few studies performed, most were reports using non-standardized multiple chemotherapeutic regimens or reports of a single regimen without comparison to the control. Further more, reports focusing on the effect of an ABVD regimen for the treatment of HD are exceedingly rare. Although ABVD is one of the most commonly used combination chemotherapy for HD in Korea, the domestic data about the effect and toxicities of ABVD compared to previously used MOPP-like regimens for Korean HD patients have not been reported until now.

In this study, we retrospectively analyzed data from HD patients diagnosed at the Korea University Medical Center to assess the treatment outcomes and toxicities of ABVD. We then compared that data to that from a historical control group treated with CVPP. CVPP is one of modified MOPP in which a less leukemogenic alkylating agent, cyclophosphamide, is substituted for mechlorethamine[12)] and in 1990s considerable proportion of HD patients were treated with CVPP combination chemotherapy in our center.

MATERIALS AND METHODS

1. Patients

The medical records from 45 patients with histologically confirmed HD at the Korea University Medical Center between March 1997 and August 2006 were reviewed and 30 of those patients treated primarily with either CVPP or ABVD combination chemotherapy were included in this study. The patients enrolled in this study were older than 16 years of age with no history of chemotherapy or radiation therapy, no previous or concurrent malignancies other than HD, at least one measurable lesion of HD, and whose follow-up duration was longer than 2 months.

2. Diagnosis and staging

The patients were classified according to the Rye histopathologic classification, including lymphocyte predominance, nodular sclerosis, mixed cellularity, and lymphocyte depletion. All patients were underwent staging investigations using the Cotswolds Committee modification of the Ann Arbor criteria,[13)] including full history and physical examination, chest radiography, computed tomography of the chest, abdomen, and pelvis, complete blood count, erythrocyte sedimentation rate, biochemistry profile, β_2-microglobulin level analysis and bilateral iliac bone marrow aspiration and biopsy. None of the cases required diagnostic laparotomy or laparoscopic evaluation.

3. Treatment schedule

Patients enrolled in this study were treated on a 28-day cycle with either CVPP or ABVD. CVPP consisted of intravenous (IV) cyclophosphamide 300 mg/m^2 with vinblastine 6 mg/m^2 on days 1, 8, and 15, and oral procarbazine 100 mg/m^2 with prednisone 40 mg/m^2 on days 1 through 10. ABVD consisted of IV doxorubicin 25 mg/m^2, bleomycin 10 mg/ m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 on days 1 and 15. Any acute adverse events related to the chemotherapy were controlled by generally acceptable supportive treatments. In all patients showing grade 4 neutropenia after chemotherapy, granulocyte colony-stimulating factor was administered with a dose of filgrastim 5 μg/kg IV until the absolute neutrophil count rebounded to 1000/mm^3. For those patients, the chemotherapeutic dose in next cycle was reduced to 75% of the original dose.

4. Evaluation of treatment outcomes and toxicities

Responses to each chemotherapy treatment were evaluated based on criteria from the Cotswolds Committee report.[13)] Complete response (CR) consisted of resolution of all disease-related symptoms and normalization of all initial physical examination, laboratory, and imaging abnormalities. A partial response (PR) was defined as a decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions. Criteria for progressive disease (PD) included a 25% or more increase in the size of at least one measurable lesion, the appearance of a new lesion, or recurrence of "B" symp-

toms which cannot otherwise be explained. The evaluation for chemotherapy-related toxicities was followed as according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) revised in August 2006.

5. Statistical analysis

Comparison of characteristics was made using the

Table 1. Baseline characteristics of the 30 eligible patients

Characteristics	CVPP		ABVD		*P*-value
	No.	%	No.	%	
Sex					.61
Female	2	18.2	5	26.3	
Male	9	81.8	14	73.7	
Age					.56
60 or older than	4	36.4	5	26.3	
Younger than 60	7	63.6	14	73.7	
Performance					.87
0~1	9	81.8	16	84.2	
>1	2	18.2	3	15.8	
Stage					.70
I/II	5	45.4	11	57.9	
III/IV	6	54.6	8	42.1	
LDH					.58
Normal	7	63.6	12	63.2	
Elevated	4	36.4	7	38.8	
β_2-microglobulin					.60
Normal	6	54.6	13	68.4	
Elevated	5	45.4	6	31.6	
ESR					.63
Normal	4	36.4	9	47.4	
Elevated	7	63.6	10	52.6	
Extranodal involve					.10
0~1	3	27.3	16	84.2	
2 or more	8	72.7	3	15.8	
B symptoms					.14
Absent	2	18.2	9	47.4	
Present	9	81.8	10	52.6	
Bulky disease					.03
Absent	11	100.0	12	63.2	
Present	0	0	7	36.8	
BM involvement					.33
Absent	8	72.7	17	89.5	
Present	3	27.3	2	10.5	
Subtypes					.71
LP	2	18.2	3	15.8	
NS	3	27.3	7	36.8	
MC	5	45.4	9	47.4	
UC	1	9.1	0	0	
Median follow-up period (months)	42.33		21.10		.07
Total	11	100.0	19	100.0	

Abbreviations: CVPP, cyclophosphamide, vinblastine, procarbazine, and prednisone; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; UC, unclassifiable.

chi-square test for binary variables and the Mann-Whitney test for continuous variables. Categorical data, such as response rates after treatment completion and treatment-related toxicities, were analyzed with a chi- square test for contingency table using the exact significance level. The overall survival time (OS) was measured from the day of diagnosis to the date of death or to the last day of follow up. The event-free survival time (EFS) was measured from the date treatment began to the date when disease progression was recognized or the date of the last follow-up visit. The rates of freedom from disease-related event and overall survival were calculated with use of the Kaplan-Meier method. The statistical significance of differences with regard to treatment regimen was assessed by the log-rank test. A P-value of less than .05 was used to indicate statistical significance. All calculations were conducted using the SPSS (version 13.0; SPSS Inc, Chicago, IL, USA).

RESULTS

1. Patient characteristics

30 patients with HD were eligible for this study. 11 patients were treated with CVPP and 19 patients received ABVD. The clinical characteristics of the patients are shown in Table 1. The two groups were well balanced regarding pre-defined stratification criteria and important prognostic factors, except that more cases with bulky disease revealing poor prognosis were included in the ABVD group.

2. Therapeutic outcomes

Response data by treatment arm are summarized in Table 2. The response rate of the ABVD group (84.21 %) was higher than that of the CVPP group (54.55 %). However, the result was not significant (P=.070). Median OS was 43.27 months (95% confidence interval [CI], 8.69 to 46.55) for CVPP and 43.17 months (95% CI, 39.79 to 46.55) for ABVD (Fig. 1A). No significant difference in median OS between the two groups was observed (P=.570). The median EFS in the CVPP group was 16.73 months (95% CI, 0 to 24.83) and was shorter than that of the ABVD group which had a median EFS of 39.03 months (95% CI, 22.95 to 55.11). However, the difference was not statistically significant (P=.088) (Fig. 1B).

Of 30 patients included in the present analysis, 7 patients in CVPP group and 4 patients in ABVD group were died. In CVPP group, 4 patients died due

Table 2. Respnse data by treatment group

Response	CVPP		ABVD	
	No.	%	No.	%
Complete response	2	18.2	9	47.4
Partial response	4	36.3	7	36.8
Stable disease	3	27.3	1	5.3
Progressive disease	2	18.2	2	10.5

Abbreviations: See Table 1.

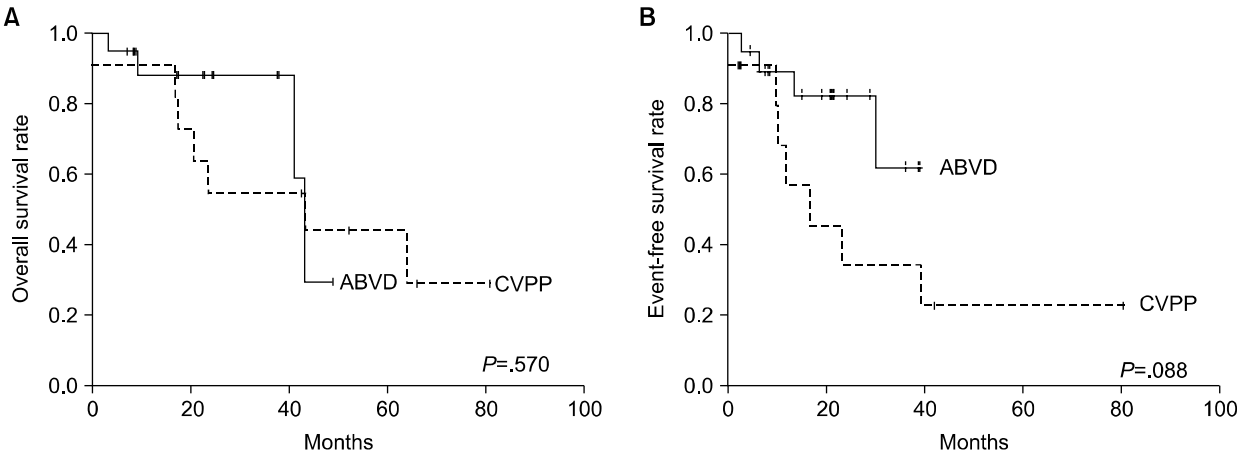

Fig. 1. Defined outcomes according to the regimens. Overall survival rate (A) and event free survival rate (B).

Table 3. Toxicity by treatment group

Type of toxcity	CVPP		ABVD		*P*-value
	No.	%	No.	%	
Neutropenia (Grade 3 or 4)	8	72.7	7	36.8	.05
Anemia (Grade 3 or 4)	2	18.2	0	0	.04
Infection (Grade 3 or 4)	2	18.2	2	10.5	.35
Cardiotoxicity (Grade 3 or 4)	1	9.1	0	0	.59
Secondary Malignancy	1	9.1	0	0	.59

Abbreviations: See Table 1.

to disease progression, but other 3 patients died due to other causes including 2 cardiac diseases and 1 vascular disease. In ABVD group, 3 cases of death were related with progression of underlying lymphoma, only 1 death was related with community-acquired pneumonia.

3. Toxicities

The treatment-related toxicity data are listed in Table 3. The proportion of patients experiencing episodes of significant (grade 3 or 4) toxicity in any cycle was analyzed. Hematologic toxicities of grade 3 or 4 were more frequently developed in the CVPP group compared to the ABVD group. Neutropenia of grade 3 or 4 was significantly higher in the CVPP group 72.72% (8/11) than in the ABVD group 36.84% (7/19) (P=.050). Anemia of grade 3 or 4 was not detected in the ABVD group, but developed in 18.18% (2/11) of the CVPP group (P=.040).

Moreover, in patients treated with the CVPP regimen followed by involved field irradiation to the mediastinum, secondary malignancy (i.e. non-Hodgkin's lymphoma, diffuse large B cell) and congestive heart failure were diagnosed during the follow up period without remnant HD. One patient in the CVPP group died from a treatment-related toxicity of hospital-acquired pneumonia developed during a neutropenic period following the first cycle of chemotherapy. Also, one case of sudden cardiac death, due to ventricular fibrillation, was developed during remission state in CVPP group. However, exact causative relationship between chemotherapy or radiation and development of life-threatening cardiac arrhythmia could not be documented because the echocardiography performed before the heart attack revealed no structural abnormality in that patient.

DISCUSSION

Since the introduction of MOPP for the treatment of HD in the 1970s,[1] the role of radiation therapy has been replaced by combination chemotherapy yielding high remission rates and satisfactory long-term survival rates. Although the reported long-term outcomes related to survival were acceptable, frequently observed late complications continued to be a major concern regarding MOPP combination chemotherapy.[14] The increased incidence of infertility and secondary hematologic malignancies, related to the administration of alkylating agents and vincristine, were not attenuated by the introduction of many therapeutic regimens containing variations of MOPP.[15] The ABVD regimen, showing no cross-resistance with MOPP, was introduced in the 1980s and yielded excellent outcomes both as a primary treatment for newly diagnosed HD and as a salvage regimen for relapsed cases following treatment with MOPP-like combination chemotherapy.[4] Although many hybrid regimens, or those alternating administration of chemotherapy using MOPP and ABVD, have been introduced, no trials have demonstrated significantly increased efficacy of multi-drug regimens over ABVD alone.[6-9] Thus, many clinical trials, to confirm the more efficient and safer regimen prevailing the ABVD combination chemotherapy, are also currently ongoing. For example, the role of novel and more in-

tensified treatment regimens such as escalating BEACOPP has been spotlighted, but these have a higher risk of treatment- related morbidities and need to be evaluated by well- controlled large-scale randomized trials with sufficient follow-up duration.[16,17]

In Korea, the ABVD regimen is one of the most commonly used combination chemotherapies in the treatment of HD. However, it is known that the incidence of HD is much lower than that of many western societies. In previously reviewed data, the incidence of HD among all malignant lymphomas was reported to be 8.6～17.8% in Korea.[10,11,18] Owing to the low incidence of disease in Korea, comparisons of HD treatment outcomes have rarely been reported. Most studies have focused upon simple reports about the treatment outcomes of a specific regimen or the course of HD following treatment regardless of the type of treatment. Ryoo et al. reported a 76% complete remission rate and an 84% five-year survival rate in 25 treatment-naïve patients with C-MOPP/ABV hybrid chemotherapy and only one case of treatment-related mortailty.[19] Another report by Ahn et al., using the identical hybrid regimen, revealed a complete remission rate of 82% and a five-year survival rate of 66.6% in 28 patients.[20] In that report, 82% of patients experienced leukopenia and infection events of grade 3 or more were detected in 29% of all patients. More recently, Cheong et al. published a single-center report of the treatment outcomes for 105 patients with HD and data from a 20-year clinical follow up wherein various chemotherapeutic regimens with or without radiation were administered.[21] While 10- and 20-year disease-free survival rates did not differ significantly among the regimens, 10- and 20-year overall survival rates were 100% in m-BACOP, 93.3% in ABVD, 76.6% in COPP/ABV hybrid, and 65.3% in C-MOPP. Thus, it was shown that an ABVD regimen was related to higher overall survival rates than the COPP/ABV hybrid or C-MOPP regimen. However, the analyses for data related to toxicities or complications after treatment were not included in the study by Cheong et al.

In this study, we found that the ABVD regimen showed significantly lower hematologic toxicities than the CVPP regimen and a trend toward better therapeutic outcomes, though this trend failed to achieve statistical significance. This result may have been due to the relatively small number of patients that were included in the analysis. In contrast, severe or life-threatening hematologic adverse events, such as neutropenia or anemia of grade 3 or 4, were detected significantly less frequently in the ABVD group than in the CVPP group although there was no difference in the method of supportive care after chemotherapy between the two treatment arms. Data showing a high rate of hematologic toxicity in MOPP-based chemotherapy have been previously reported.[22,23] Even in hybrid regimens, wherein a lower dose of ABVD is combined with MOP, the incidence of neutropenia is higher, compared to ABVD alone.[8] High rates of toxic events may be thought indirectly related to poor therapeutic outcomes. Delays in or dose reduction of chemotherapeutic agents due to severe neutropenia compromise dose intensity and so may jeopardize outcomes by providing tumor cells the chance to develop secondary resistance. There has been some evidence for better outcomes in HD with maintenance of dose intensity[24] and so the low dose intensity rate secondary to grade 3 or 4 neutropenia in the CVPP group may have contributed to the inferior therapeutic outcomes.

There are some limitations in this study, and so some degree of caution is required to interpret the result of this analysis. The structural limitation secondary to retrospective design could not be overcome, because the follow-up durations were short and the population numbers included in each treatment arm were relatively small. However, it is not easy in actuality to assess the outcomes and toxicities of ABVD combination chemotherapy with prospective comparative study including a large number of patients, given the lower incidence of HD in Korean population. Despite these limitations, the present study might have significance in that there has been no previous study in Korea comparing ABVD, most commonly used chemotherapy for HD, to the chemotherapeutic regimens used in the past, such as MOPP and its variant forms. Namely, the results of this

study using domestic data can offer objective evidences proving the superiority of current standard regimen to those used in the past. Also, considering that novel regimens for HD, such as Stanford V and BEACOPP, have been tried and shown encouraging results recently,[16,17] ABVD may not be generally accepted as one of the optimal treatment options for HD any more in the future. So this study can be the basic data for subsequent development of new standard regimen that can replace ABVD by overcoming its limitations. Therefore the implication of this study is that constitutional data of larger population with continuous long-term follow-up by many centers will be needed so as to evaluate the efficacy and toxicity of chemotherapy for HD more accurately and to establish the most suitable chemotherapeutic regimen for Korean HD patients.

According to this study, ABVD for HD showed significantly lower hematologic toxicities and moderately better treatment outcomes than did CVPP. Because HD is known to be sensitive to chemotherapy and radiation, the vast majority of patients can experience long-term disease-free survival. As such, not only the treatment efficacy itself but also treatment-related toxicities and late complications such as infertility and secondary malignancies should be taken into account. Further study is warranted to establish more efficient and less toxic combination chemotherapies for HD.

요 약

배경: 저자들은 ABVD를 이용한 복합항암화학치료를 받은 호지킨병 환자들의 치료 성적과 독성을 분석하고, 이를 과거에 CVPP에 의한 항암화학치료를 시행받았던 환자군과 비교하고자 하였다.

방법: 1997년부터 2006년까지 고려대학교 의료원에서 조직학적으로 진단된 호지킨병 환자들을 대상으로 하여 그중 일차적 치료로 ABVD 혹은 CVPP의 복합 항암화학치료가 시행된 환자들의 의무기록을 후향적으로 분석하였다.

결과: 본 연구에는 총 30명의 환자가 포함되었으며 이 중 19명은 ABVD로, 11명은 CVPP로 치료를 받았다. 치료에 대한 반응률은 ABVD군과 CVPP군에서 각각 84.21%와 54.55%로 나타났다. 중앙 생존기간은 ABVD군이 43.17개월, CVPP군이 43.27개월이었으며 (P=.571), 무진행생존기간은 ABVD군이 39.03개월, CVPP군이 16.73개월로 나타났다(P=.088). 비록 중앙 생존기간 및 무진행생존기간에 있어서는 양 군 간의 유의한 차이가 존재하지 않았지만 혈액학적 독성의 발생은 ABVD군에서 유의하게 낮았다. 3도 이상의 호중구 감소증이 CVPP군에서는 72.72%에서 나타났지만 ABVD군에서는 36.84%에서만이 관찰되었다(P=.050).

결론: 호지킨병에 대한 항암화학치료로서 ABVD는 CVPP에 비해 유의하게 낮은 혈액학적 독성과 함께 유의하지는 않지만 전반적으로 우월한 치료 성적을 나타냈다.

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