Cancer Chemother. Pharmacol. 2, 101–105 (1979)

Cancer Chemotherapy and Pharmacology

Prolonged Disease-Free Survival in MOPP-Resistant Hodgkin's Disease after Treatment with Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD)

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Summary. *Twenty-one patients with advanced Hodgkin's disease resistant to MOPP (mechlorethamine, vincristine, procarbazine, prednisone) were treated with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). ABVD induced complete remission in 13 patients (62%) and partial remission in 2 (9.5%). In particular, complete response to ABVD was obtained in 7 of 13 patients who failed to respond to primary MOPP chemotherapy. After six cycles, no further therapy was given to patients in complete remission. At 36 months from starting ABVD, 69.7% of complete responders remain alive and free of disease, with a total survival of 73.4%. In contrast, none of the patients in whom partial response or nonresponse was observed was alive at 18 months. ABVD for six cycles was accompanied by mild and reversible toxicity. The results indicate that there is no cross-resistance between MOPP and ABVD. ABVD appears a simple, effective, and tolerable multiple-drug chemotherapy for use in patients who are resistant to MOPP.*

Introduction

The introduction of combination chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) dramatically improved the prognosis of advanced Hodgkin's disease. Intensive cyclic therapy with MOPP induces complete remission (CR) in 70%–80% of patients who are either previously untreated [8] or in relapse following extensive radiotherapy [5]. In their 10-year report, De Vita et al. [9] showed that 66% of the initial 80% who had entered CR achieved a prolonged disease-free status with no maintenance treatment. Lokich et al. [16] have estimated that in 72% of patients Hodgkin's disease is not controlled definitively by MOPP. However, the recent results of Fisher et al. [10] indicate that patients relapsing after a CR induced by MOPP are not necessarily resistant to MOPP. In 32 patients retreated with MOPP, a second CR was induced in 56%. However, while 60% of patients whose initial CR was longer than 12 months had a prolonged disease-free survival, this occurred in only 18% of those with an initial CR lasting less than 1 year. Therefore, an alternative treatment is indicated for patients not entering on a first CR with MOPP or relapsing within 12 months from an initial CR.

ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) is a new multiple-agent chemotherapy specifically designed in 1973 as an alternative treatment for MOPP failures [3]. Drug selection was determined by the demonstrated activity of each compound as single agent in Hodgkin's disease refractory to conventional drugs, the synergistic activity between adriamycin and dacarbazine, the little evidence of cross-resistance in humans between vincristine and vinblastine, and the absence of overlapping toxicity. The therapeutic activity of ABVD in advanced Hodgkin's disease was tested against that of MOPP in a previous controlled study [2, 3] where the incidence of CR after six cycles was found to be comparable (70% vs 62%). Following the early experience achieved in the above-mentioned study, where a cross-over treatment between MOPP and ABVD was carried out in patients who showed resistance to either combination, we have continued to administer ABVD in patients who are refractory to MOPP. This paper reports the results obtained with ABVD in 21 MOPP-resistant patients.

Patients and Methods

Twenty-one consecutive patients with a histologically proven diagnosis of Hodgkin's disease were suitable for evaluation of the response after secondary treatment with ABVD (Table 1). Histopathologic

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0344-5704/79/0002/0101/$ 01.00

Table 1. Main characteristics of patients

Total	21
Median age (years)	35 (24–65)
Sex M/F	9/12
Performance status	> 60
Histological subgroups	LP 2, NS 12, MC 2, LD 5
Previous therapy	
MOPP only	8
MOPP and radiotherapy	13
Extension prior to ABVD	
Nodal	13
Extranodal ± nodal	8
Symptoms prior to ABVD	A 5, B 16
Median duration of disease prior to ABVD	16 months (6–101)

Table 2. Characteristics of MOPP-resistant patients responding to ABVD

	No.	CR	PR
Total	21	13	2
Systemic symptoms			
A	5	4	–
B	16	9	2
Extension			
Nodal	13	10	1
Extranodal	8	3	1
Lung	4	1	1
Bone	1	1	–
Marrow	1	1	–
Liver	1	0	–
Breast	1	0	–

classification and pathologic staging according to the Ann Arbor system were determined at the time of initial diagnosis. All patients were considered to be resistant to MOPP therapy given at full or nearly full doses, since they showed either progressive disease during treatment (primary failures) or relapse within 6 months of its discontinuation. Thirteen patients had also received prior extensive radiotherapy. All patients had a performance status greater than 60. The median age was 35 years (range: 24–65). There were 9 males and 12 females. Histological subgroups were as follows: lymphocytic predominance (LP) 2, nodular sclerosis (NS) 12, mixed cellularity (MC) 2, and lymphocytic depletion (LD) 5. Prior to the start of ABVD, the disease was limited to lymph nodes in 13 patients, while extranodal involvement (± nodal extension) was clinically or histologically documented in 8. Most patients presented with systemic symptoms (A 5, B 16). The median interval between the diagnosis and the start of ABVD therapy was 16 months (range 6–101).

In the ABVD regimen all four drugs were injected IV every 15 days. The doses (mg/m^2 body surface) were as follows: adriamycin 25, bleomycin 10, vinblastine 6, and dacarbazine 375. A dose-reduction schedule was utilized in the presence of a leukocyte count of less than 4,000/mm^3 and/or a platelet count of less than 130,000/mm^3, determined on the day of drug injection. The details of dose adjustment were identical with those reported in a previous study [3]. In patients who achieved CR, treatment was stopped after six cycles. A patient was considered to be in complete remission when all symptoms and signs of disease had disappeared for a minimum of 1 month. Besides the return to normal of biochemical and radiologic parameters, a second biopsy of known involved extralymphatic sites such as liver and bone marrow had to be interpreted as negative. Partial remission (PR) was defined as 50% or greater reduction in the product of the longest perpendicular diameter of all sites of measurable disease. Patients with regression of less than 50% were categorized as nonresponders.

Results

Table 2 presents the characteristics of patients showing a response to ABVD. CR was documented in 62%, PR in 9.5%. The median time to CR was 2 months (range 1–6 months). The observed response rate was not related to age, sex, or histological subgroups. The remission rate was higher in patients without (80%) than in those with systemic symptoms (56%), and in cases with nodal (77%) than in those with extranodal (37.5%) extension. As shown in Table 3, in the present series the incidence of CR was higher in patients whose previous treatment had been MOPP alone (75%) than in patients previously treated with MOPP plus radiotherapy (54%). It is also worthy of note that ABVD induced CR in more than half the patients (7 of 13) showing progressive disease during primary therapy with MOPP.

Table 3. Response to ABVD related to previous treatment

	No.	Response to ABVD		
		CR	PR	None
MOPP alone	8	6	2	–
MOPP + RT	13	7	0	6
Response to primary MOPP ± RT				
CR	5	4	0	1
PR	3	2	0	1
None	13	7	2	4

RT = Radiotherapy

Six of 13 patients achieving CR refused to complete six cycles of ABVD. In two patients nausea and vomiting were considered intolerable, while in four patients there were no particular reasons for discontinuation of chemotherapy except the psychological desire to be off any kind of treatment. In patients receiving an incomplete course of ABVD, two relapsed after 5 and 13 months. In contrast, relapse was documented after 7 months in only one of seven complete responders who had completed six cycles of chemotherapy.

Figures 1 and 2 illustrate the actuarial duration of remission and overall survival 3 years from starting ABVD therapy. Ten of 13 complete responders have remained continuously free of disease from a minimum of 6$^+$ to a maximum of 45$^+$ months after the start of

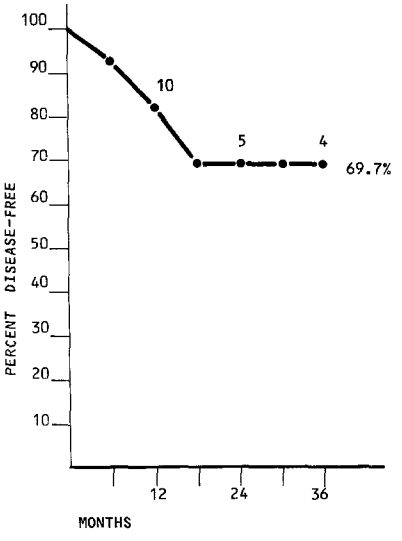

Fig. 1. Disease-free survival from beginning of ABVD

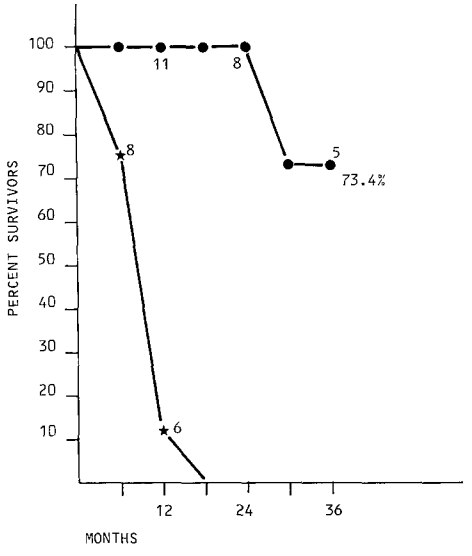

Fig. 2. Overall survival from beginning of ABVD. ●—●: complete responders; ★—★: partial responders and nonresponders

ABVD therapy. Survival of complete responders is significantly longer than that of nonresponders. Two patients died outside the Institute for reasons unrelated to Hodgkin's disease (acute gastroenteritis and myocardial infarction). These two patients were in CR for 6 and 34 months, and they are accounted for in Figure 2 according to the rules of the actuarial methods [19].

Reversible leukopenia and thrombocytopenia were observed in 47.5% and 52% of patients, respectively. In no patient was a leukocyte count of under 1,500/mm^3 and/or a platelet count of under 50,000/mm^3 documented. No patient developed severe bacterial infection during or after ABVD therapy. Nausea and vomiting occurred in all cases but these symptoms were pronounced only in four patients. Eleven patients showed marked hair loss and four presented peripheral neuropathy secondary to vinblastine. No patient showed symptoms and signs of adriamycin cardiomyopathy or of bleomycin pulmonary toxicity. Mild skin hyperpigmentation occurred in three patients. In those who had completed six cycles of ABVD, the average total doses for the individual drugs were: adriamycin 70%, bleomycin 95%, vinblastine 70%, dacarbazine 84%.

Discussion

Although this is a small series, we believe that the results are of practical importance. Our findings clearly indicate that ABVD is effective in producing CR in more than 50% of patients resistant to optimal primary chemotherapy with MOPP. Even more important, CR was followed by a prolonged disease-free survival with no maintenance treatment, recorded 3 years from the start of secondary chemotherapy. The initial objective response occurred promptly and in most patients a marked regression was already evident within a few days of the first drug administration. The treatment was simple to administer in the outpatient clinic and was devoid of any significant morbidity. Two patients could not tolerate the treatment because of vomiting. This well-known undesirable side effect of most polydrug regimens can be, at times, more pronounced with ABVD therapy because the combination includes adriamycin and dacarbazine. The ABVD regimen has recently been applied in our Institute in more than 100 patients, either combined with radiotherapy for the treatment of intermediate stages of Hodgkin's disease [18] or sequentially, alternated with MOPP in stage IV disease [4]. In these series, no patient refused to complete six cycles of ABVD because of intolerable nausea and vomiting. The results of ABVD in MOPP-resistant Hodgkin's disease in limited series of patients were recently reported by four groups [6, 7, 12, 20]. The high response rate was confirmed by Vicente and Cortes [20], who have utilized the original dose schedule in primary MOPP failures. In the other series the incidence of CR was definitely inferior. In our opinion, the difference was attributable to a number of factors, such as low performance status, extensive prior therapy including some of the ABVD basic components, lower dose schedule, and high incidence of extranodal (e.g., marrow) involvement. We believe that, to be effective, a MOPP salvage program such as ABVD therapy must be administered as soon as a patient is considered to be MOPP-resistant, i.e., while the performance status is still relatively good and the bone marrow reserve not severely compromised by prior therapy.

Table 4. Comparison of regimens effective in MOPP failures

Combination	No. cases	CR + PR	CR	Reference
VLB	29	18	2 (7%)	[22]
BLM, CCNU	22	13	2 (9%)	[13]
ADM, CCNU	10	8	5 (50%)	[23]
CCNU, VLB, BLM (CVB)	39	33	10 (26%)	[11]
ADM, BLM, VLB, DTIC (ABVD)	21	15	13 (62%)	This study
BLM, VLB, ADM, STZ (BVDS)	10	5	3 (30%)	[21]
BLM, CCNU, ADM, VLB (B-CAVe)	22	17	11 (50%)	[17]
STZ, CCNU, ADM, BLM (SCAB)	17	10	6 (35%)	[14]
BLM, DTIC, VCR, PRD, ADM (B-DOPA)	15	12	9 (60%)	[16]
ADM, DTIC, BLM, CCNU, PRD (ABDIC)	22	15	5 (23%)	[15]

In recent years, the original MOPP chemotherapy regimen has been modified in a number of studies by deletion, substitution, or addition of its basic components. However, none of the modified MOPP regimens was convincingly superior as far as incidence and duration of CR was concerned when results were retrospectively compared with those obtained with MOPP [1]. Therefore, MOPP still remains the most useful combination available as well as the simplest and safest regimen for the primary treatment of advanced Hodgkin's disease. As mentioned in the introduction, MOPP failures account for a total of about 50%—65%, and retreatment by the same regimen yields a very low response rate in patients relapsing within 12 months from initial CR [10]. When advanced Hodgkin's disease does not show any response to optimal primary chemotherapy or relapses within 6 months from an initial CR, it is invariably fatal within a short time in most patients. For this reason, in the past few years several research institutions have engaged in pilot studies to establish new effective regimens for MOPP-refractory patients (Table 4). Although, the small number of patients evaluable in each reported series is one of the factors that accounts for the differences in the response rate, the combinations yielding the highest incidence of CR and the longest duration of both remission and survival were ABVD (62%), B-DOPA [16] (60%), and B-CAVe [17] (50%). However, while after B-DOPA (bleomycin, dacarbazine, vincristine, prednisone, adriamycin) the maximum reported duration of CR was 21^+ months and that after B-CAVe (bleomycin, CCNU, adriamycin, vinblastine) was 35^+ months, that observed after ABVD in this series was 48^+ months. Probably because of either intensive prior treatment including radiotherapy or the administration of experimental agents, most MOPP salvage programs often involved severe, and even fatal, toxicity due to prolonged myelosuppression [11, 13, 14, 21], sepsis and bleeding [11, 14—16, 21], renal tubular dysfunction secondary to streptozotocin [14], bleomycin pneumonitis [6, 13, 14], and adriamycin cardiomyopathy [17, 23]. In particular, this last side effect was observed in two patients treated with B-CAVe, probably because of the high single dose of adriamycin (60 mg/m^2). Therefore, some of the above-mentioned regimens cannot always be recommended for general use. In contrast, with the ABVD program no severe or delayed side effects have so far been documented. In particular, we have no evidence that the myocardial infarction that caused the death of one patient could in fact be a clinical sign of ADM cardiomyopathy.

In conclusion, ABVD appears to be a useful, tolerable, and simple multiple-drug chemotherapy for use in patients with primary resistance or early relapse after MOPP therapy. The high response rate achieved with this new combination in the primary treatment of advanced Hodgkin's disease [2, 3] suggests that attempts should also be made to administer ABVD alternately with MOPP to improve the incidence and the duration of an initial CR. The preliminary results of a controlled study with MOPP versus MOPP plus ABVD in stage IV patients have already revealed that sequential therapy utilizing noncross-resistant combinations has improved the incidence of CR as well as the 2-year disease-free and overall survival [4]. If confirmed, these findings would further expand the indications for the treatment of Hodgkin's disease with ABVD, since useful results can be obtained with about half the cumulative toxic dose of adriamycin and of bleomycin.

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Received August 3, 1978/Accepted November 22, 1978