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Treatment of MOPP-resistant Hodgkin's Disease with Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD)*

G. PAPA,† F. MANDELLI,† A. P. ANSELMO,† A. M. DE LUCA,† R. MAURIZIENRICI,‡ F. MAURO,† A. M. TESTI,† S. AMADORI† and C. BIAGINI‡

†*Institutes of Hematology and* ‡*Radiology, University of Rome, Italy*

Abstract—*ABVD chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine) was given in monthly courses to 20 patients with Hodgkin's disease resistant to MOPP. Complete responses were achieved in* 10 *of the* 18 *evaluable patients* (55%). *Responses occurred rapidly with a median of* 3 months. *Nine of the* 10 *complete responders are presently off all therapy and remain disease-free after* 9–60 months. *The actuarial median survival for all patients is* 38 months. *Toxicity caused by ABVD was acceptable. ABVD is a useful salvage chemotherapy program for patients with Hodgkin's disease resistant to MOPP.*

INTRODUCTION

MOPP (MECHLORETHAMINE, vincristine, procarbazine and prednisone) is the most widely used chemotherapeutic regimen in previously untreated patients with advanced Hodgkin's disease. Complete remission rates of 60–80% have consistently been reported, with approximately 50% of patients alive and free of disease after five and ten years [1]. Unlike the success of primary chemotherapy, the treatment of patients who fail to respond or relapse after MOPP has not been as successful. Treatment with cytotoxic drugs that are active against Hodgkin's disease but not included in MOPP would probably be of benefit in these patients. The combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) has been reported by Santoro and Bonadonna [2] to be effective in a proportion of patients with MOPP-resistant Hodgkin's disease. Seventy-one per cent of those treated responded; 62% achieved a complete remission, with 69% of complete responders remaining alive and relapse-free at 36 months.

We report here our experience with ABVD in the salvage treatment of MOPP-resistant Hodgkin's disease.

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MATERIALS AND METHODS

Patients

A total of 20 patients with histologically documented diagnosis of Hodgkin's disease were entered in this study between January 1976 and March 1981. Two patients were considered non-evaluable since they did not complete 3 courses of therapy because of early death due to causes unrelated to their disease or ABVD (rupture of an intra-abdominal aortic aneurysm; cerebrovascular accident). The characteristics of the remaining 18 evaluable patients are shown in Table 1.

All patients had received extensive MOPP therapy (median number of cycles 6, range 4–16); four patients had also received prior extensive radiotherapy. All patients were considered MOPP-resistant since they all either showed progressive disease while on MOPP (15 patients) or relapsed within 12 months of completing MOPP (3 patients, relapse after 10, 11 and 11 months). Prior to the start of ABDV, extent of disease work-up included physical examination, complete blood count, liver function tests, chest and abdominal X-ray, bone marrow aspirate and biopsy. In selected patients, skeletal survey, bone and liver scans, lymphoangiogram and biopsies of affected organs when appropriate were done. The Lukes–Butler [3] histopathologic classification was used and the patients were staged according to the Ann Arbor convention [4]. The ABVD regimen was administered every four weeks and consisted of adriamycin (25 mg/m^2 i.v.), bleomycin (10 mg/m^2 i.v.), vinblastine (6 mg/m^2 i.v.) and dacarbazine (375 mg/m^2 i.v.) on days 1 and 15. A dose reduction schedule was utilized in the presence of a leukocyte count of less than 4000/mm^3, determined on the day of injection (Table 2). All patients were treated with a maximum of six monthly cycles. ABVD was discontinued if the patient's disease clearly progressed during treatment. Complete remission (CR) was defined as disappearance of all evidence of disease by physical examination, X-ray and blood chemistries. Furthermore, a second biopsy of accessible extranodal sites of known involvement had to be interpreted as negative. Partial remission (PR) was defined as greater than 50% reduction in tumor mass for one month or more. Patients with disease regression of less than 50% were classified as non-responders. Curves of the probability of survival and disease-free survival were calculated from the initiation of ABVD by the life-table method [5]. Differences between the curves were evaluated by the generalized Wilcoxon test [6].

RESULTS

Complete remission was achieved in 10 of 18 patients (55%) on ABVD. No responses were observed in the remaining 8 patients. The median time to CR was 3 months (range 2–6 months). Patients who had CR did not differ significantly in age, sex, histology and duration of prior disease (Table 1). Responses were

Table 1. Clinical data of MOPP-resistant patients and their responses to ABVD

	Complete responders	Non-responders
No. patients	10	8
Male/Female	7/3	7/1
Median age (range, yr)	29 (13–56)	28 (10–48)
Histology		
Nodular sclerosis	2	3
Mixed cellularity	4	3
Lymph predominance	1	0
Lymph depletion	3	2
Prior treatment		
MOPP only	8	6
MOPP + Radiotherapy	2	2
Response to primary MOPP		
Complete remission	3	0
Failure	7	8
Extent of disease*		
Nodes	7	6
Lung	1	1
Bone	2	1
Breast	1	0
B symptoms*	1	4
Median duration of disease prior to ABVD (months)	18	18

*Prior to ABVD.

Table 2. Attenuation schedule

WBC/mm^3	Platelets/mm^3	Dose adjustment
> 4000	> 130,000	100% all drugs
3999–3000	129,000–100,000	50% adriamycin vinblastine
2999–2000	99,000–80,000	50% dacarbazine 25% adriamycin, vinblastine
1999–1500	79,000–50,000	25% dacarbazine no adriamycin, vinblastine
< 1500	< 50,000	100% bleomycin hold other drugs

noted with similar frequency in patients with nodal (53%) and extranodal disease (66%). In the two patients presenting with bone lesions prior to ABVD, the second biopsy repeated at the end of treatment was interpreted as negative. The response rate was lower in patients presenting with B symptoms at the time of ABVD (20% vs 69%). Remission duration and survival curves are shown in Figs 1 and 2. Nine out of 10 complete responders are presently off all therapy and remain disease-free 9–60 months after initiation of ABVD. The median survival time for the entire population of patients was 38 months (range 9–61 months); survival was significantly prolonged in responders ($P < 0.01$). All patients were able to be treated as outpatients. The toxic complications are reported in Table 3. All patients experienced varying degrees of nausea and vomiting, which appeared to be tolerated since no patient refused to continue therapy. Some degree of alopecia was seen in most patients. No patient developed significant drug-induced

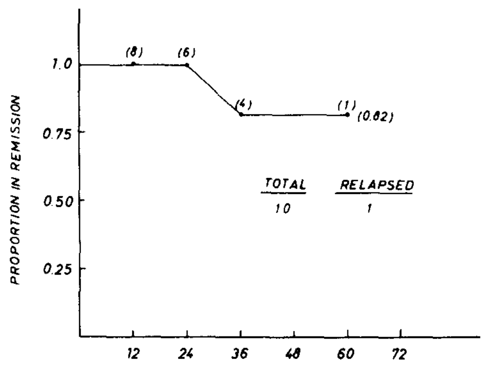

Fig. 1. Actuarial relapse-free survival from start of ABVD. Numbers in parentheses represent patients at risk at given times.

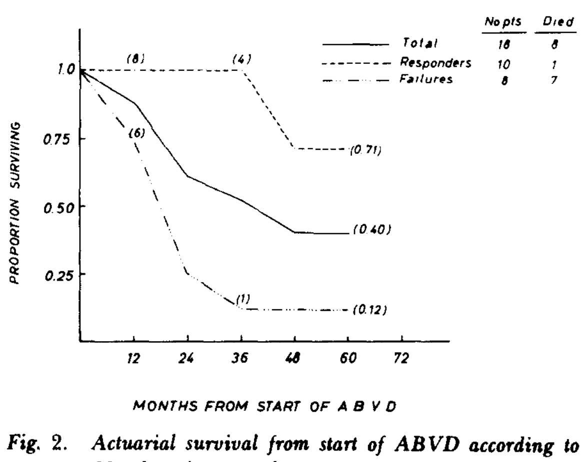

Fig. 2. Actuarial survival from start of ABVD according to response. Numbers in parentheses represent patients at risk at given times.

Table 3. Toxic manifestations

Leukopenia*	66%
Thrombocytopenia*	16%
Herpes zoster	39%
Alopecia	72%
Nausea–vomiting	100%
Paresthesias	11%

*WBC < 4000/mm^3; platelets < 130,000/mm^3.

neuropathy or cardiomyopathy. Bone marrow toxicity of ABVD was not excessive. Transient leukopenia and thrombocytopenia were observed in 66 and 16% of patients respectively. In no instance was a leukocyte count of less than 1000/mm^3 and/or a platelet count of less than 100,000/mm^3 recorded. No patient had a life-threatening bacterial infection during ABVD; there were seven episodes of herpes zoster which resolved in all cases without complications. Table 4 presents the percentage of calculated drug dose administered per cycle. Responders and non-responders were able to tolerate similar amounts of drugs.

DISCUSSION

Although based on a small series of patients, the results of the present study clearly indicate that ABVD is an effective drug combination for MOPP-resistant Hodgkin's disease. Complete remission was achieved in 55% of the patients, with 82% of the responders projected alive and relapse-free at 60 months. Several years more follow-up is needed to determine whether these remissions will truly be durable, however. The protocol is simple and easy to administer on an outpatient basis. Toxicity was generally mild and consisted primarily of gastrointestinal symptoms and alopecia. Myelosuppression has been moderate without serious consequences. The high response rate and the potential for long-term disease-free survival with ABVD in MOPP-resistant Hodgkin's disease confirms the results recently reported by Santoro and Bonadonna [2] and Vicente and Cortés Funes [7]. In contrast, other groups [8, 9] were less successful in treating MOPP-resistant patients with ABVD. In agreement with others [2, 10], we believe that the discrepancy in the results reported with ABVD is probably related to major differences in patient characteristics in the various trials, such as performance status, extent of prior therapy, duration of prior disease, incidence of B symptoms and extranodal involvement. As suggested by Straus *et al.* [10], future trials with salvage chemotherapy in Hodgkin's disease resistant to first-line treat-

Table 4. Percentage of calculated drug dose administered per cycle

Drug	Cycle 1	2	3	4	5	6
Adriamycin	85	70	74	72	62	79
Bleomycin	100	100	100	100	100	100
Vinblastine	77	73	70	78	61	74
Dacarbazine	85	78	83	83	68	78

ment should include a careful evaluation of the patient characteristics in order for the data to be correctly interpreted and compared. In conclusion, ABVD appears to be an effective regimen with tolerable toxicity for the salvage of patients with Hodgkin's disease who have failed primary MOPP chemotherapy, particularly for those with minimal extranodal disease and no B symptoms. Its activity warrants further assessment not only as salvage chemotherapy for patients failing MOPP, but also, following the preliminary results reported by Bonadonna *et al.* [11], as a primary treatment alternative to MOPP.

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