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Adriamycin, Bleomycin, Vinblastine and Imidazole Carboxamide (ABVD) Therapy for Advanced Hodgkin's Disease Resistant to Mustine, Vinblastine, Procarbazine and Prednisolone (MVPP)

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Summary. *Forty-one previously treated patients with advanced Hodgkin's disease were treated with a combination chemotherapy regimen – ABVD (adriamycin, bleomycin, velbe/vincristine, imidazole carboxamide). Complete remission was achieved in three patients (7%), partial remission in 23 (56%), and no response in 15 patients (37%). The median survival of the group was 12 months from the start of therapy. Survival correlated with response to treatment. No apparent benefit resulted from giving more than six courses of therapy (3 months' treatment time). There was no serious haematological toxicity in patients without bone marrow disease, and bleomycin and adriamycin toxicity was not apparent clinically or at autopsy in the dosages employed in the regime. Alopoecia was very frequent.*

The role for ABVD, other than as a primary induction regimen, appears to be in conjunction with other regimens in the induction of patients with adverse features at presentation or during induction; or in the salvage and palliation of patients who demonstrate a response but fail to achieve remission, either initially or at relapse, with MOPP (mustine, vincristine, procarbazine, and prednisolone) or MVPP (mustine, vinblastine, procarbazine and prednisolone.

The ABVD Regimen for Advanced MVPP-Induced Hodgkin's Disease

Patients with Hodgkin's disease who fail to remit with primary induction therapy, or who relapse after an initial chemotherapy-induced remission, present a major problem in management. This may occur in approximately 40%–50% of patients with advanced Hodgkin's disease [9, 16]. Continuation of primary therapy in the face of progressive disease is valueless; similarly, a lower response rate is seen after relapse (Sutcliffe et al., submitted for publication) when the initial regimen is reapplied [10]. The introduction of a new combination regimen (adriamycin, bleomycin, velbe, imidazole carboxamide: ABVD) with a lack of mutual cross-resistance with MOPP was reported by Bonadonna et al. in 1975 [1]. Encouraged by initial reports of the use of this regimen for primary induction of remission, we investigated the ABVD regimen in patients with disease resistant to MVPP, either during primary induction or at relapse.

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Patients

Forty-one patients were studied between 16. 12. 74 and 31. 3. 78. There were 30 males and 11 females with an age range of 8–56 years (mean 33 years, median 34 years). Three children (ages 8, 14, and 14 years) were included. All had received MVPP chemotherapy as the primary form of treatment, whilst others were given MOPP or CCNU with or without bleomycin before commencing ABVD. Some patients had undergone irradiation for localised disease before commencing initial chemotherapy, and some received palliative irradiation before receiving ABVD. Patients were allocated to receive ABVD when disease progression occurred despite chemotherapy with MVPP, either during initial remission induction or following relapse. Certain patients commenced ABVD after an exacerbation of disease that had remained apparently stable after the failure to achieve complete remission with MVPP. All chemotherapy was administered at St. Bartholomew's Hospital and follow-up information was complete on all patients, either to death or to 1. 7. 78.

Methods

Histological sections of diagnostic biopsies were reviewed (A.G.S.) and classified according to standard nomenclature [14]. In many cases repeat biopsies were undertaken to confirm the diagnosis of disease progressing through initial chemotherapy. The stage of disease was assessed by accepted criteria [5].

In 38 adult patients the regimen consisted of adriamycin 25 mg/m^2, bleomycin 10 mg/m^2, vincristine 1.5 mg/m^2 (or vinblastine 6 mg/m^2) and imidazole carboxamide 350 mg/m^2. Vincristine was used in those patients in whom MVPP was the former treatment, and

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vinblastine was substituted following MOPP therapy. All four agents were given in a fast-running infusion on a 14-day cycle. The three children were given the same drugs but were given IV therapy on days 0 and 7, with a 14-day interval between successive courses. Prednisolone was given PO on medical indications when considered appropriate.

The majority of patients had chemotherapy administered on an outpatient basis. Full blood counts were checked before each injection. All patients underwent assessment of lung function and 12-lead cardiography prior to treatment. These tests were repeated in patients surviving to the completion of a planned six courses of treatment.

Three forms of response to therapy were accepted:

1. Complete Response. The return of all symptoms and signs of disease to normal for a period of not less than 3 months. Further, all nonoperative investigations had to be within normal limits (including ESR 30 mm/h), and extranodal sites of disease prior to treatment were rebiopsied when possible following treatment to establish ablation of disease.

2. Partial Response. The failure to achieve a disease-free state for more than 3 months; or the reduction of symptoms, signs or investigational evidence of disease.

3. No Response. The failure to modify the symptoms, signs or investigational evidence of disease.

Twenty-four patients received either additional chemotherapy or irradiation after the failure of attempts to control the disease with ABVD.

Information was abstracted from patient's notes. The survival curve was drawn according to the actuarial method of Kaplan and Meier [11].

Results

1. Histology and Stage of Patients at Commencement of ABVD

There were 31 patients with nodular sclerosing histology (76%), four patients with mixed cellularity (10%), four with lymphocyte depletion (10%) and one each with lymphocyte-predominant or unclassifiable Hodgkin's disease.

Thirty-eight patients (93%) had Stage IVB disease. The remaining three patients had Stage IB, IIIB, or IVA disease. Three patients were Stage IV by virtue of extranodal extensions (pelvic wall) (two) or brachial plexus (one). Two had distortion of the normal anatomy of the stomach, duodenum and pancreas without endoscopic evidence of mucosal invasion. The remaining 34 had evidence of dissemination, at one extranodal site in 18, at two sites in 15, and three or more sites in one.

2. Number of Courses Administered

Four patients died between the first and second courses of treatment without evidence of response. Three received two courses and showed evidence of disease progression. Death occurred shortly after the second course in one, and the remaining two were given alternative therapy. One patient received three courses and died inexplicably at home whilst showing evidence of response. Three patients received four courses of treatment and had progressive disease requiring alternative therapy. Three patients received five courses. Partial response was noted in two. However, one declined further treatment and one absconded temporarily before the sixth course could be given. One showed no evidence of response and died shortly after the fifth course. Twenty-seven patients received the planned six courses and nine of these had further injections up to a total of 12 courses. Thus, eight of 41 were given between one and three courses, and 33 of 41 received between four and 12 courses.

3. Response to ABVD

A complete response was achieved in three patients (7%), a partial response in 23 (56%), and no apparent response in 15 patients (37%). The response to ABVD according to the previous response to MVPP is shown in Table 1.

The seven patients who failed to show a response to MVPP also failed to respond to ABVD. However, 13 of 19 (68%) patients with partial responsiveness to MVPP also showed similar sensitivity to ABVD, and two (10.5%) achieved a complete response to ABVD, having failed to do so with MVPP. Only one of 15 initial complete remitters with MVPP achieved a similar state with ABVD. However, ten (66%) showed continuing drug sensitivity as judged by the achievement of a further partial response. Four of 15 (26%) who initially responded completely to MVPP were unresponsive to subsequent treatment with ABVD.

None of the patients with disease progression through ABVD achieved control with subsequent chemotherapy or irradiation, and no patient who had attained partial remission with ABVD achieved a complete remission with subsequent alternative therapy.

Table 1. Response[a] to ABVD according to response to MVPP

Response to ABVD	CR		2	1	3
	PR		13	10	23
	NR	7	4	4	15
		7	19	15	41
		NR	PR	CR	
		Response to MVPP			

[a] CR, complete remission; PR, partial remission; NR, no response

4. *Survival From Commencement of ABVD*

The median survival of the group was 12 months from the start of therapy (Fig. 1). Twenty-four patients (59%) have died, and 17 remain alive at follow-up periods of 4–35 months.

There was no clear correlation between the length of history of Hodgkin's disease and survival following ABVD (Fig. 2). Survival was clearly related to response. Only one of the 15 unresponsive patients remains alive at 29 months; the median survival of the remaining 14 was 4.25 months. Thirteen patients achieving a partial response are alive at 4–30 months of follow-up. The median survival of those who are dead was 10 months. All three patients achieving complete remission remain alive at 12, 27, and 35 months.

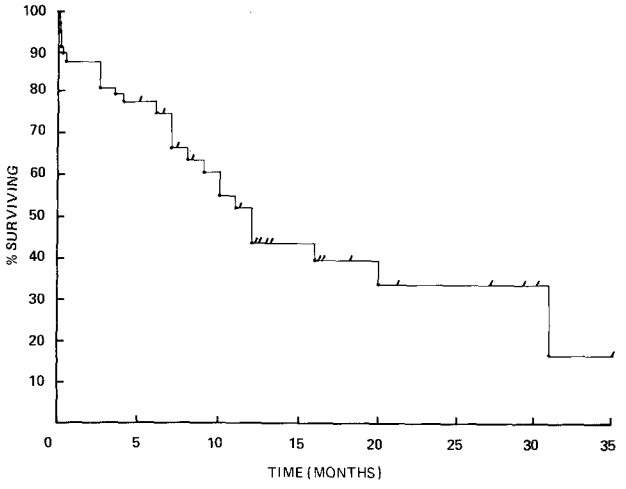

Fig. 1. Survival from commencement of ABVD therapy for advanced Hodgkin's disease

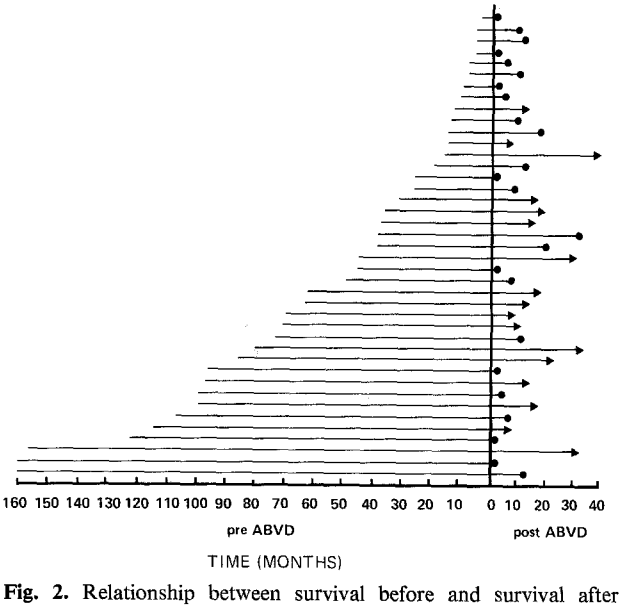

Fig. 2. Relationship between survival before and survival after ABVD. —●, dead; ——→, alive

Survival was also related to the number of courses administered. However, in all patients receiving three courses or less the reason for this was either death or disease progression. Response was not related to the number of courses in those receiving more than four courses. In particular, there did not seem to be any additional benefit if more than six courses were given.

5. *Toxicity*

All patients suffered some degree of alopoecia, the majority sustaining sufficient hair loss to warrant the wearing of a wig. Nausea and vomiting occurred in all for up to 4 h after injection. Fit patients tolerated outpatient administration satisfactorily. However, several patients were admitted overnight for treatment, either by request or as a result of their general debility. The subjective impression of many patients was that the ABVD regimen was not as unpleasant as the MVPP regimen. However, this was in part due to the 3-month administration time, compared with 9 months for the MVPP regimen.

Haematological toxicity was assessed according to the lowest haemoglobin (Hb), total white count (WBC), and platelet count observed during treatment. Four patients with bone marrow involvement and abnormal peripheral blood counts prior to treatment have been excluded; the analysis is thus restricted to 37 patients, two of whom had marrow disease without modification of their peripheral blood count. The mean Hb was 10.7 g% (range 8.0–14.1 g%), WBC 4.6 $\times$ 10^9/litre (range 1.0–10.2) and platelets 251 $\times$ 10^9/litre (range 36–723). Blood transfusions were given as necessary on medical indication. Supportive care in terms of therapeutic or prophylactic granulocyte or platelet transfusions was not required.

No patient suffered clinical lung damage as a result of bleomycin. Lung function tests were available in 23 patients who survived six or more courses. The interpretation is complex, as 15 had pre-existing abnormalities related to pulmonary Hodgkin's disease and correction of variations in Hb level were not applied. However, eight patients had a slight reduction of gas transfer that could be attributed to bleomycin.

Adriamycin cardiotoxicity was not clinically apparent in any patient and all 24 electrocardiograms taken after treatment showed either those changes apparent before adriamycin administration or changes consistent with progressive Hodgkin's disease (usually sinus tachycardia).

6. *Mortality*

Twenty-four of the 41 patients (59%) are dead; postmortem examinations were performed in 16 of these.

Hodgkin's disease was the principal cause of death in 23, although in one the autopsy revealed concurrent pneumocystis carinii pneumonia. Varicella zoster pneumonia was the direct cause of death in one patient who had achieved a good response to ABVD. No autopsy examination revealed evidence of either cardiac damage or lung damage that could have been attributed to the drugs administered.

Discussion

The reports of Bonadonna et al. indicate that ABVD is probably as effective as MOPP/MVPP as an induction regimen and will induce complete remission in approximately 70%–75% of patients with advanced Hodgkin's disease who have not received previous chemotherapy [1, 3]. It is also apparent that in conjunction with radiotherapy, the complete response rate for both regimens can be improved to approximately 90% [3, 6]. When both regimens are used concurrently in induction of either untreated extranodal disease [3] or advanced nodal and extranodal disease at presentation or late relapse [6] a response rate of 81%–100% is achieved, and this is in excess of the response rate achieved with MOPP or ABVD used alone.

However, in MOPP-resistant patients and those in post-chemotherapy relapse the situation is somewhat different. In the initial report [1], no evidence for mutual cross-resistance was found, on the basis of objective response after crossing to the alternative regimen. A later report noted that 11 of 18 MOPP-resistant patients achieved complete remission (61%) that was well maintained after ABVD [15]. Using a modification of this regimen (ABVD), Case reported one complete remission and 15 objective responses in 24 patients with advanced MOPP-resistant Hodgkin's disease [7].

A 33% complete remission rate was recorded by Vicenti and Cortes-Funes in 15 previously treated patients [17], and Clamon and Corder [8] observed only one partial response in nine patients with extensively treated Stage IV disease. In this paper we record three complete responses (7%) and 23 partial responses (56%) in 41 previously treated patients, 38 of whom had Stage IVB disease.

Our report suggests the existence of cross-resistance between the two regimens, and supports our previous conclusion that patients whose disease progresses through MVPP achieve little benefit from a change in chemotherapy (Sutcliffe et al., submitted for publication). Of importance, however, are the two patients who achieved a complete remission with ABVD after having failed to do so with MVPP, and the additional benefit after changing therapy in 13 patients achieving a partial remission with MVPP. In addition, a further complete remission and ten partial responses were seen in 15 patients who achieved initial remission with MVPP. Thus, in 34 patients who demonstrated initial chemo-sensitivity, 26 (76%) showed further responsiveness after a change of chemotherapy. Thus, in this situation of salvage after initial chemotherapy failure, the complete remission rate of 7%, although low, is greater than that achieved with single agents in our experience (although not in that of others) [2], and the overall response rate is of the same order as those achieved with the most effective single-agent and combination regimens.

It might be argued that the four patients dying after the first course should be excluded, as the regimen could not be fully assessed in the period available. However, we have been impressed with the marked clinical improvement that can occur within 24 h with this regimen, and so they have been kept in the report. One feature in favour of the regimen is the rapidity of response when it occurs, and the response should be largely achieved by four courses (2 months). It was our experience, however, that incomplete responses were rarely followed by periods of stable disease activity, and that rapid exacerbations were common.

The toxicity of the regimen was acceptable within the limits of an otherwise poor prognosis. Alopoecia was the most distressing feature, although all surviving for greater than 6 months acquired further hair growth. With the drug dose and cycle administration used here, no concern about lung or myocardial damage need be expressed in patients without pre-existing disease at these sites.

There are thus two aspects of the disease–treatment relationship expressed here. The results accord with our previous experience, in that primarily chemotherapy unresponsive Hodgkin's disease tends to remain so despite a change in chemotherapy. This appears to be a property of the disease rather than of the chemotherapy available. It remains to be seen whether further chemotherapeutic modifications about which encouraging reports are emerging (B-Dopa [13], BVDS [18], SCAB [12]) will endorse this conclusion. Paramount importance in the assessment of response of a new regimen attaches to the constitution of the group under study, particularly in terms of stage, extent of extranodal disease, and response to previous therapy, as these factors will clearly modify both response rate and survival. Further, the criteria for complete and objective response may clearly modify the results obtained by different groups.

The other aspect concerns the role of the ABVD regime in the management of advanced Hodgkin's disease. In spite of the good response rate in untreated patients, we feel that the toxicity and the absence of information about long-term follow-up do not support the use of ABVD as a primary induction regimen at the moment.

Similarly, our experience of the lack of response in patients with disease that progresses through MVPP therapy suggests that other agents or regimens (including radiotherapy) should be tried in this situation, which carries a very short prognosis. The high remission rate achieved with the concurrent use of MOPP and ABVD [3] may, however, indicate the use of this approach in patients who are not progressing through MOPP/MVPP induction at a satisfactory rate, but before evidence of regrowth occurs; or in those who are likely to have a lower remission rate with MVPP alone, i.e., in elderly patients and in the presence of bulky stage IVB disease and multiple extranodal sites of involvement. There also appears to be a role for ABVD in patients who fail to achieve complete remission with MOPP or MVPP, either initially or in relapse, but have demonstrable sensitivity in terms of disease reduction with MVPP or other agents. The response rate in this situation is good (15 of 19 patients: Table 1), and remission is achieved rapidly and with acceptable side effects.

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