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Combination chemotherapy for the treatment of Hodgkin's disease in relapse

Results with lomustine (CCNU), melphalan (Alkeran), and vindesine (DVA) alone (CAD) and in alternation with MOPP and doxorubicin (Adriamycin), bleomycin, and vinblastine (ABV)

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Summary. *Vindesine (desacetyl vinblastine amide sulfate, DVA) was used in combination with CCNU (lomustine) and melphalan (Alkeran) (CAD) to treat 15 heavily pretreated patients with Hodgkin's disease in relapse. The patients were treated with up to six cycles, depending upon their response. Two patients (13%) achieved a complete remission (CR) and five (33%) patients a partial remission (PR). The major toxicity was prolonged thrombocytopenia, which was decreased by a reduction in the initial drug doses for patients who had received extensive prior chemotherapy and radiotherapy (RT). The CAD regimen was then alternated with nitrogen mustard or cyclophosphamide, vincristine, procarbazine, and prednisone (MOPP, C-MOPP) and doxorubicin (Adriamycin), bleomycin, and vinblastine (ABV) for a total of nine cycles in 25 patients with Hodgkin's disease in relapse with somewhat more favorable prognostic features. Two patients also received low-dose RT to areas of bulky nodal disease. Eleven patients (44%) achieved a CR and seven (28%) a PR. Of the 11 CR patients, six remain in remission. The serious toxicity was comparable to that seen with other combination chemotherapy regimens. These results indicated that the CAD/MOPP/ABVD regimen is as active as other so-called 'salvage' regimens for Hodgkin's disease in relapse, and suggest that it might be useful for newly diagnosed Hodgkin's disease.*

Introduction

The treatment of Hodgkin's disease patients in relapse following combination chemotherapy is usually less successful than that of those in whom the condition is newly diagnosed. Attempts have been made to develop new drug combinations which are non-cross-resistant with MOPP [18] for these patients. Since the results with such combinations have varied widely, we have continually tested new drug combinations to improve upon our own results [22]. An additional impetus to this search for new 'salvage' chemotherapy regimens has been the use of potentially non-cross-resistant drug regimens at the outset for newly diagnosed patients. Our results with MOPP/ABVD/low-dose radiotherapy (RT) has improved upon our own experience with MOPP alone for untreated patients with advanced Hodgkin's disease [21, 23]. The treatment of the small number of patients relapsing after such treatment, however, has been problematic. Four of 26 heavily pretreated Hodgkin's disease patients who had received vincristine and vinblastine responded to vindesine [20]. For this reason vindesine was combined with CCNU and Alkeran (CAD). Neither of the latter two agents, both of which have proven efficacy in Hodgkin's disease [13, 26, 27], has been employed in our protocols as primary treatment. There is experimental evidence in mouse leukemias and plasmacytomas that tumors resistant to one alkylating agent or nitrosourea might be sensitive to another [16, 19]. The same is true for human multiple myeloma [1]. This observation has successfully been applied in the M-2 protocol which contains cyclophosphamide, melphalan, and carmustine (BCNU) in combination with vincristine and prednisone. This regimen has improved the survival of patients with multiple myeloma over that obtained with single alkylating agents [12].

It was hoped that the CAD combination would prove to be effective in patients relapsing after or failing MOPP or MOPP/ABVD. The use of the alternating MOPP/ABVD schedule proved to be as successful as other salvage regimens for heavily pretreated Hodgkin's disease patients [21, 22]. Once we were satisfied that CAD was an active combination, we then alternated CAD with MOPP and ABV as a salvage treatment program. Dacarbazine was omitted from ABVD because of its association with severe nausea and vomiting.

Materials and methods

Starting in December, 1978, 15 patients with Hodgkin's disease in relapse were treated with the CAD regimen. This consisted of CCNU (lomustine) 100 mg/m^2 PO on day 1, Alkeran (melphalan) 6 mg/m^2 PO on days 1–4, and DVA (vindesine) 3 mg/m^2 IV on day 1 and day 8. Patients were recycled every 5–6 weeks for up to six cycles of treatment depending upon the response. In February, 1979 a new protocol which alternated CAD with two drug regimens was begun. The MOPP and C-MOPP regimens were those described by DeVita et al. [4]: nitrogen mustard 6 mg/m^2 (limit 10 mg) or cyclophosphamide 650 mg/m^2 IV, vincristine 1.4 mg/m^2 (limit 2 mg) IV on days 1 and 8, and procarbazine 100 mg/m^2 (limit 150 mg) PO on days 1–14. Prednisone 40 mg/m^2 on days 1–14 was also given with the first two MOPP cycles. The second regimen was similar to our own modification [3] of the ABVD regimen of Santoro et al. [18], with the omission of dacarbazine: doxorubicin (Adriamycin) 25 mg/m^2 IV, vinblastine 6 mg/m^2 (limit 10 mg) IV on days 1 and 14, and bleomycin 2 mg SC daily on days 4–12 and 18–26. The patients were taught to administer bleomycin SC to themselves using $^5/_8$-inch, 25-gauge needles and 1-ml TB syringes. CAD was administered first, followed

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Table 1. Dosage attenuation schedule

WBC	Platelet count		
> 4,000	> 150,000	100%	doses
3,000–3,900	100,000–149,000	100%	VCR, bleo, pred, dacarb
		50%	VLB, DVA, Alkeran, HN2, Adria, CCNU
2,000–2,900	50,000– 99,000	100%	bleo, pred, VCR
		50%	dacarb
		25%	DVA, VLB, Alkeran, HN2, Adria Hold CCNU
1,500–1,999	50,000	100%	bleo
		50%	VCR
		25%	DVA, VLB, Alkeran, HN2, Adria, dacarb Hold CCNU
< 1,500	< 50,000	Hold therapy, re-evaluate in 1 week	

VCR, vincristine; bleo, bleomycin; pred, prednisone; dacarb, dacarbazine; VLB, vinblastine; HN2, nitrogen mustard; Adria, Adriamycin

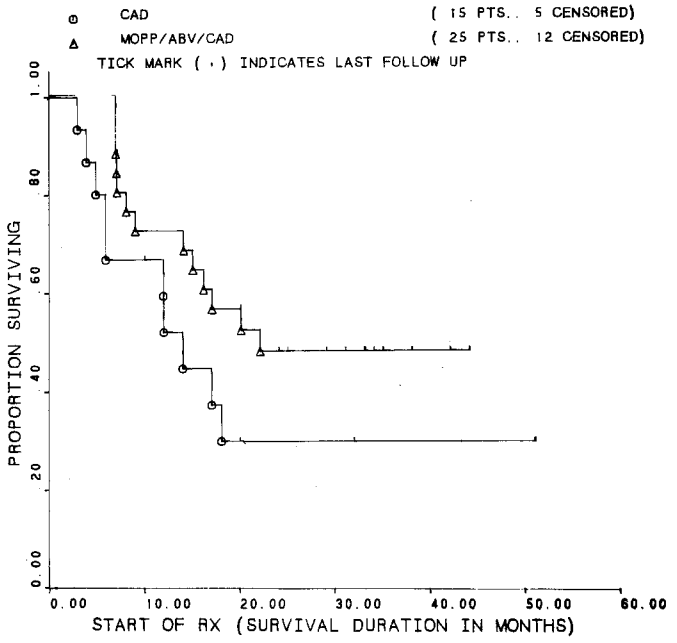

Fig. 1. Survival in months of relapsed Hodgkin's disease patients treated with CAD and MOPP/ABV/CAD, counting from the date of initial salvage treatment. $P = 0.141$

by (C-) MOPP on days 36–43. ABV was administered on day 28 following (C-)MOPP, and CAD was then recycled on day 28 following ABV. Three alternating cycles of each regimen were administered, to give a total of nine cycles. Twenty-five evaluable patients with Hodgkin's disease have been entered on this protocol, 23 of whom received no RT as part of the program while two patients received approximately 2,000 rads over $2^1/_2$ weeks to nodal areas involved with disease between cycles 6 and 7.

The doses of the drugs were attenuated when patients were leukopenic or thrombocytopenic, according to the dose schedule shown in Table 1. In addition, the initial doses of CCNU and melphalan were lowered by 25%–50% in patients who had received extensive prior chemotherapy and RT.

A CR was defined as the disapperance of all measurable disease parameters during treatment for at least 1 month. A partial remission (PR) was deemed to be a diminution in the size of all measurable disease parameters by > 50% for at least 1 month. A minor response (MR) was a decrease in measurable disease parameters by 25%–50% or more for less than 1 month. Performance status was assessed as described by Karnofsky [10]. Toxicity, including severe nausea and vomiting, was documented by review of the patients' medical records.

Survival cures were constructed according to the product limit method of Kaplan and Meier [9] and the differences between them assessed according to the log-rank test [17].

Results

CAD

The characteristics of the patients treated with CAD are shown in Table 2. A total of 15 patients were entered. The median age was 28 years, with a range of 18–59 years. Two-thirds of the patients had nodular sclerosis histology. Four of the other patients had mixed cellularity and the fifth was not subclassified because the diagnosis was obtained by mediastinoscopy from a small fragment of tissue. Two-thirds of the patients had extranodal sites of relapse prior to the initiation of CAD. Of the 15 patients, 13 (87%) had B symptoms when they were started on CAD. Most of the patients were failing treatment before they were started on CAD, and the longest disease-free interval was 17 months. In all, 13 of the 15 patients had previously been treated with extended-field RT and chemotherapy. Nine had received MOPP/ABVD (ABV) and four, MOPP alone. These patients were treated relatively late in the course of their disease. The median time from initial diagnosis to initiation of CAD was 49 months.

The results are shown in Table 3. There were only two CRs (13%). One of these occurred in the single patient who had received RT only and no chemotherapy. The toxicity was acceptable (Table 4). One patient developed sepsis during a period of neutropenia. CAD had to be discontinued in four of the early patients because of prolonged thrombocytopenia. All four had received extensive prior chemotherapy and RT, and this problem was subsequently eliminated by an attenuation of the initial doses of lomustine and melphalan, as mentioned above. Of the 15 patients treated with CAD, 10 have died, and the median survival is 14 months from the start of CAD treatment (Fig. 1).

Table 2. Patient characteristics

	CAD group	CAD/MOPP/ABV group
Total patients	15	25
Age (years)		
Median	28	23
Range	18–59	17–53
Sex		
Male	11 (73.3%)	10 (40%)
Female	4	15 (60%)
Histology		
Nodular sclerosis	10 (66.6%)	20 (80%)
Mixed cellularity	4 (26.6%)	2 (8%)
Lymphocyte predominance	0 (0.0%)	1 (4%)
Unclassified	1 (6.6%)	1 (4%)
Lymphocyte depletion	0 (0.0%)	1 (4%)
Sites of relapse		
Nodal only	5 (33.3%)	13 (52%)
Extranodal only	2 (13.3%)	3 (2%)
Extranodal + nodal	8 (53.3%)	9 (36%)
Bone	1	1
Liver	3	1
Lung	7	7
Pleura	1	1
Subcutaneous	1	3
B symptoms	13 (87%)	20 (80%)
Performance status	5 (70), 6 (80)	1 (50), 4 (70)
(Karnofsky)	4 (90)	10 (80), 10 (90)
Disease-free interval		
Prior to salvage treatment (months)		
Median	0	5
Range	0–17	0–51
Prior treatment		
Chemo only	1 (6.6%)	3 (12%)
RT only	1 (6.6%)	5 (20%)
Chemo & RT	13 (86.6%)	17 (68%)
MOPP or MOPP variant only	4 (26.6%)	17 (68%)
MOPP + ABVD (ABV)	9 (60.0%)	0
Time between initial diagnosis and salvage treatment (months)		
Median	49	19
Range	4–121	3–107

Table 3. Results of treatment

	CAD group	CAD/MOPP/ABV group
No. of patients with	15	25
CR	2 (13.3%)	11 (44%)
PR	5 (33.3%)	7 (28%)
Minor or no response	5 (33.3%)	0
Disease progression	3 (20.0%)	7 (28%)
Relapses from CR (remission duration in months)	1 (4)	5 (3, 6, 9, 13, 21)

CR, complete remission; PR, partial remission

Table 4. Toxicity

	CAD group	CAD/MOPP/ ABV group
Total no. of patients	15	25
Toxic event		
WBC < 2,000/mm^3	2	13 (52%)
Sepsis	1 (7%)	3 (12%)
Epistaxis	0	1 (4%)
Severe constipation	1 (7%)	4 (16%)
Paralytic ileus	0	1 (4%)
Severe paresthesias	1 (7%)	4 (16%)
Jaw pain	0	1 (4%)
Orthostatic hypotension	0	1 (4%)
Severe nausea and vomiting	1 (7%)	5 (20%)
Mouth sores	1 (7%)	1 (4%)
Severe alopecia	0	1 (4%)
Drug rash	0	2 (8%)
Platelet count < 80,000/mm^3	7 (47%)	14 (56%)

CAD/MOPP/ABV

Twenty-five patients were treated with CAD/MOPP/ABV (Table 2). The median age was 23 years, with a range of 17–53 years. Twenty of the 25 patients (80%) had nodular sclerosing histology. The histology was not subclassified in one patient because of the poor quality of the original biopsy material.

Thirteen of the 25 patients (52%) had only nodal sites of relapse. Twenty of the 25 patients had B symptoms when they started therapy with CAD/MOPP/ABV. In contrast with most of the patients treated with CAD, the majority of patients were treated in relapse with CAD/MOPP/ABV rather than during progression of disease, with a median disease-free interval of 5 months (range 0–51 months). Seventeen patients (68%) had previously received combination chemotherapy, usually with MOPP or a variant of MOPP, and extended-field RT. The patients were treated with CAD/MOPP/ABV earlier in the course of their disease than with CAD. The median time from initial diagnosis to salvage treatment was 19 months (range 3–107 months).

The response rate is shown on Table 3. Eleven of 25 patients (44%) achieved a CR, and five of these patients have relapsed. Eight of the 11 CRs were in patients with B symptoms. The CR rate was slightly higher for patients with a disease-free interval ≥ 11 months than for those with a disease-free interval < 11 months ($P = 0.09$, Fischer Exact Test). Three of five patients who had received prior RT only achieved a CR.

The toxicity of CAD/MOPP/ABV was acceptable and was comparable to that of CAD. There were no instances of prolonged pancytopenia. There were three episodes of sepsis related to neutropenia, and one patient developed epistaxis with thrombocytopenia. The incidence of vinca alkaloid-related neuropathy was slightly higher for CAD/MOPP/ABV than for CAD alone. It was reversible in all cases except for the patient with orthostatic hypotension. One patient developed a mild paralytic ileus while on MOPP. A drug rash, probably related to procarbazine, occurred in two patients. Severe nausea and vomiting, as reported by the patients and documented in their records, was relatively infrequent with CAD/MOPP/ABV, and was less than that seen with ABVD or MOPP/ABVD [18, 21, 22]. Of the 25 patients, 13 have died; the median survival is 22 months from initiation of treatment.

Discussion

The salvage combination chemotherapy of patients with relapsed or primary treatment-resistant Hodgkin's disease has met with varying success. As we have suggested previously, variations in reported results even with the same regimen may be due to a difference in the prognostic factors of the patients who are treated [22]. The CR rates for ABVD have varied between 4% and 59% [3, 11, 14, 18, 22, 25], due largely to these differences. In our analysis of the results reported in the literature with ABVD and our own results with ABVD and MOPP/ABVD, several prognostic features emerged. The most important was the presence of some disease-free interval prior to treatment with the salvage regimen. With both MOPP/ABVD and MOPP, a disease-free interval of longer than 11–12 months was a favorable prognostic feature in predicting a CR [6, 22]. A second important prognostic factor was the time during the course of the disease that the patients received the salvage treatment. Patients treated after multiple relapses did not fare as well as those treated relatively early in the course of their disease [22]. A third prognostic factor was the sites of disease activity or relapse prior to salvage treatment. Patients with exclusively nodal sites tended to respond better than those with extensive extranodal involvement. Two other factors that have been found to be important for all types of Hodgkin's disease treatment are performance status and presence or absence of B symptoms. Santoro et al. found that exclusively nodal sites of disease and absence of B symptoms were significantly favorable prognostic factors in their analysis of their own results with ABVD [18]. The results in the two trials reported here must be discussed in the context of these prognostic factors.

The 50% total response rate even with only two CRs (13%) among the heavily pretreated patients, a high proportion of whom had multiple unfavorable prognostic factors, indicated that CAD is an active combination. Most of these patients were treated relatively late in the course of their disease, as reflected in the median time between initial diagnosis and salvage treatment of 49 months. In most of them the disease was progressing with whatever treatment they were receiving prior to CAD. One third of the patients had a performance status of only 70. Two-thirds had extranodal sites of disease, and 87% had B symptoms.

The CAD regimen, which contains a nitrosourea and an alkylating agent, caused serious prolonged myelosuppression when given repeatedly in full doses. For that reason, the doses of lomustine and melphalan are now attenuated in patients who have been extensively pretreated with chemotherapy and RT when CAD is used alone or in alternation with MOPP and ABV. The other toxicity was minor, and only one of 15 patients reported severe nausea and vomiting.

The CAD combination is active in patients who have previously received other combination chemotherapy. All of the seven patients who achieved a CR or a PR with CAD had received at least the MOPP drug combination, with the exception of the one CR patient who had only received RT. Five of the responding patients had received ABVD as well as MOPP. Although these results are suggestive, the number of patients is too small to fully assess the degree of non-cross-resistance of CAD with MOPP and ABVD.

We were next prompted to try CAD in alternation with MOPP and ABV because of these results with CAD alone and our success with MOPP/ABVD in patients relapsing after MOPP. The higher CR rate of 44% in the CAD/MOPP/ABV trial reflects the more favorable prognostic factors of the patients treated in that trial. The patients were treated relatively early in the course of their disease, at a median of 19 months after initial diagnosis. Most had some disease-free interval prior to treatment with CAD/MOPP/ABV, and there was a trend toward a higher CR rate for those with a disease-free interval of 11 months or longer. Three of five patients who had only received prior RT achieved a CR with CAD/MOPP/ABV. The CR rate for similar patients was 69% with MOPP/ABVD [21, 23]. The patients who received prior chemotherapy had MOPP or a variant of MOPP, and none had MOPP/ABVD. Over one half of the patients had exclusively nodal sites of relapse. The performance status was 80–90 in 80% of the patients.

In this small group of patients with relatively favorable prognostic factors, the 44% CR rate with CAD/MOPP/ABV is not significantly different from the 50% CR rate we achived with MOPP/ABVD [21, 22] or the 59% CR rate reported by Santoro et al. with ABVD [18], although this group may have treated more truly MOPP-resistant patients. The median follow-up time is 20 months (range 7–44 months) for CAD/MOPP/ABV, and the median remission duration has not yet been reached. With ABVD Santoro et al. [18] achieved a median remission duration of 17 months at a median follow-up time of 12.5 months (range 5–79 months). With the relatively small numbers of patients and the differing total follow-up

times, it is likely that the median survival of 22 months and total survival with slightly less than 50% with CAD/MOPP/ABV is comparable to the median survival of 27 months and overall survival of 32.4 months at 5 years for ABVD reported by Santoro et al. [18].

The toxicity of CAD/MOPP/ABV was acceptable. Approximately one half of the patients experienced severe transient leukopenia and thrombocytopenia, associated with sepsis in three patients and epistaxis in one other. In no instance was the myelosuppression prolonged.

A definite advantage of CAD/MOPP/ABV was the relatively low incidence of severe nausea and vomiting. This was reduced by the omission of dacarbazine from ABV and the substitution of cyclophosphamide for nitrogen mustard. Dacarbazine was omitted from ABV because, considering its toxicity, the evidence for its importance as a single agent in Hodgkin's disease is meager [7]. There are several published reports of variants of MOPP in which cyclophosphamide has been substituted for nitrogen mustard with comparable results to MOPP [2, 15]. Nausea and vomiting are almost always seen with MOPP and are particularly severe with ABVD [18]. In the MOPP/ABVD/low-dose RT program for patients with advanced Hodgkin's disease [21], 12% of patients discontinued treatment before receiving three courses, and 29% discontinued maintenance treatment because of this side-effect.

Two of the 25 patients in the CAD/MOPP/ABV trial received low-dose (2,000–3,000 rads) adjuvant RT to areas of bulky nodal disease between the 6th and 7th cycles of chemotherapy. Both patients had received no prior RT. The RT was added because such bulky areas of nodal disease are likely sites of further relapse after chemotherapy alone [8]. The use of low-dose RT as an adjunct to combination chemotherapy seems usually to be sufficient to prevent subsequent relapse in these areas [5, 21, 23].

In conclusion, the CAD regimen seems to be active against Hodgkin's disease in relapse following treatment with MOPP and ABVD, even among patients with a relatively poor prognosis. The alternation of CAD with MOPP or C-MOPP and ABV, with or without additional low-dose radiotherapy, is an effective program for patients with Hodgkin's disease in relapse, with results that are comparable to other salvage chemotherapy regimens including MOPP/ABVD [21] and ABVD [18] if the prognostic factors of the patients are considered. The toxicity of the CAD/MOPP/ABV program is comparable to that of other salvage regimens [18, 21]. The omission of dacarbazine and the substitution of cyclophosphamide for nitrogen mustard greatly decrease nausea and vomiting compared with ABVD or MOPP/ABVD. In view of these encouraging results, a randomized trial comparing CAD/MOPP/ABV/low-dose RT for newly diagnosed advanced-stage Hodgkin's disease patients is currently in progress [24].

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