



Combined modality therapy in advanced Hodgkin's disease: a report on 218 patients with a median follow-up of eight years

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ABSTRACT

Background and Objective. This study was designed to evaluate the efficacy and toxicity of monthly alternating ABVD/MOPP compared to ABVD/OPP regimens in patients with advanced stage Hodgkin's disease (HD), as well as in early stage patients with systemic symptoms and/or bulky disease.

Design and Methods. 218 patients with previously untreated HD entered this study: 106 patients in arm A (ABVD/MOPP) and 112 in arm B (ABVD/OPP). Patients received eight courses of one of the two regimens after stratification according to the stage. Patients in complete remission (CR) received 20 Gy to the involved field and 40 Gy to the spleen. The actuarial survival curves were performed according to Kaplan and Meier.

Results. No statistically significant differences were observed between the two arms in terms of CR rate and toxicity. However, analysis of total relapses revealed that patients treated with ABVD/OPP had a significantly higher likelihood of achieving a second CR compared to patients who entered the ABVD/MOPP arm.

Interpretation and Conclusions. both schemes of chemotherapy followed by radiotherapy produce high percentages of CR, low risk of relapse and an acceptable toxicity.

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Key words: chemotherapy, Hodgkin's disease, radiotherapy, secondary neoplasm, toxicity

Despite the favorable results achieved by means of chemotherapy for the treatment of advanced stage Hodgkin's disease (HD), different issues still remain unresolved. The most relevant remains the fact that the cure rate only approximates 50% of patients treated with standard first-line treatment.

Independently from the time from the first complete remission (CR), the survival rate for patients

treated with conventional second-line chemotherapy for relapsed HD does not exceed 25%.^{1,2}

In order to improve the number of patients cured from HD, cyclic alternating chemotherapy protocols were designed according to the Goldie-Coldman hypothesis about the spontaneous tendency of neoplastic cells to mutate to a resistant phenotype. As a consequence of this, the best approach to overcome resistance in clinical trials was considered the use of alternating cycles of noncross-resistant combinations such as MOPP and ABVD.³⁻⁵ The possibility of inducing long-term complications by the use of mutagenic agents especially alkylating-containing regimens alone or in association with radiotherapy, represents another controversial aspect in the evaluation of results achieved with protocols for the treatment of HD. The persistence of gonadal function impairment affects the quality of life of the patients and the risk of developing secondary acute leukemias, non-Hodgkin's lymphomas (NHL) or solid tumors lowers the overall survival curve in patients in persistent CR.⁶⁻⁹

In 1983, we started a prospective study to test the impact on the therapeutic response and survival duration of the monthly alternating ABVD/MOPP regimen compared to ABVD/OPP in patients with advanced stage HD as well as in early stage patients with systemic symptoms and/or bulky disease. In the ABVD/OPP combination chemotherapy the MOPP regimen was modified by eliminating mechlorethamine in an attempt to reduce the incidence of late complications, such as secondary tumors and infertility.¹⁰ In both arms, consolidation radiotherapy was delivered on the involved field (20Gy) and on the spleen (40Gy). The results of this study, with a median follow-up of 108 months, are illustrated in this paper.

Materials and Methods

From February 1983 to October 1991, 218 consecutive patients affected by previously untreated HD entered this study: 106 patients in arm A (ABVD/MOPP) and 112 in arm B (ABVD/OPP). Histologic classification was performed according to Lukes and

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Butler.¹¹ On the basis of the Ann-Arbor classification patients were clinically staged with physical examination, complete blood cell count and differential, erythrocyte sedimentation rate (ESR), serum biochemistry, bone marrow biopsy, standard chest x-ray, computed tomography (CT) of the chest and abdomen.¹² Bulky mediastinum was defined as a mass larger than one third of the thoracic diameter and bulky nodal sites as lesions with a maximal transverse diameter greater than 7 cm. Bulky disease was present in 24% of all patients in arm A and 21% in arm B. Eighty-one (76%) and eighty (71%) patients were staged III B and IV in arm A and B, respectively.

The date of this analysis was December 1996. In arm A, alternating ABVD/MOPP was administered according to the standard regimen designed by Bonadonna *et al.*³ In arm B, ABVD was alternated to OPP as in the ABVD/MOPP regimen.¹² The OPP scheme was administered as follows: vincristine 1.4 mg/sqm i.v. on days 1, 8 and 15; procarbazine 100 mg/sqm orally on days 1 to 21; prednisone 40 mg/sqm orally on days 1 to 14 and tapered on days 15 to 21. The MOPP scheme: mechlorethamine 6 mg/sqm i.v. on days 1 and 8; vincristine 1.4 mg/sqm i.v. on days 1 and 8; procarbazine 100 mg/sqm orally on days 1 to 14; prednisone 40 mg/sqm orally on days 1 to 14 and tapered on days 15 to 21. A standard course of ABVD was administered (Table 1). The maximum single dose of vincristine given in OPP or MOPP was 2 mg. Patients were randomly allocated to receive 8 courses of one of the two regimens after stratification according to the stage. In both arms, drug administration was delayed seven days when white blood cells were less than 2,300/mm³ and platelets less than 100,000/mm³. A calculation of the doses of each of the 8 drugs delivered during the ABVD/MOPP and ABVD/OPP program was carried out retrospectively and was expressed as percent of the optimal dose. Patients who achieved a CR received a 20 Gy involved field radiotherapy to the previously affected sites and 40 Gy to the spleen using a 6 MeV linear accelerator with a 200 cGy daily fractionated dose for five days/week.

Criteria for response

Patients were evaluated for clinical response after four and eight courses of chemotherapy and 4 weeks after the end of radiotherapy. CR was defined as the complete disappearance of all clinical evidence of disease with normalization of blood values including ESR and imaging tests. Patients with persistent radiologic residual abnormalities in the absence of other signs of active disease were considered in CR. A partial response (PR) was defined as a decrease greater than 50% in the largest diameter of all measurable and assessable lesions with disappearance of symptoms. Failure was defined as an absence of tumor response, a decrease of less than 50% in the largest diameter of all measurable lesions or progression of disease.

Relapse was determined on the basis of clinical and radiological evidence of recurrence, and confirmed histologically whenever possible.

Statistical analysis

The actuarial survival curves were performed according to Kaplan and Meier.¹⁴ Relapse-free survival (RFS) was calculated from CR to relapse. Overall survival (OS) was measured from the time of entry into the study to the time of the last examination. Event-free survival (EFS) took into account failure during the treatment, as well as relapse or toxic deaths. For descriptive and univariate statistical analysis, Fisher's exact test and log-rank test were used as appropriate. Kaplan-Meier survival curve estimates were considered and subgroup compared by log-rank test.¹⁵

Finally, in order to evaluate multivariate relations, Cox's proportional hazard model was used to investigate the prognostic value of the following factors: age, sex, bulky disease, mediastinal bulky disease, lung involvement, number of affected sites, ESR or treatment.

Results

A total of 218 patients not previously treated were randomized after stratification for age and stage. The patients' characteristics are listed in Table 1. Of the 218 patients, 106 were randomly assigned to

Table 1. Patient characteristics.

Characteristic	MOPP/ABVD		OPP/ABVD	
	no.	%	no.	%
No. of patients	106		112	
Men	60	57	64	57
Women	46	43	48	43
Age				
> 40	28	26	33	30
< 40	78	74	79	70
Stage				
IB	2	2	4	3.5
IIB	23	23	28	25
IIIB	46	43	41	37
IVA	8	8	12	11
IVB	27	25	27	24
Histology				
PL	2	2	5	4
SN	51	48	50	45
CM	42	40	43	38
DL	11	11	12	11
Bulky disease	26	24	24	21
ESR				
> 40	29	27	23	20
< 40	77	73	89	79

Table 2. Results.

	MOPP/ABVD		OPP/ABVD		Total	
	no.	%	no.	%	no.	%
N° of pts evaluable	106	112	218			
CR	97	92	99	88	196	90
Failure	9	8	13	12	22	10
Relapse	20	20	15	15	35	16
Deaths	28	26	19	17	47	21
OS at 14 years of follow-up		72		82		78
RFS at 14 years of follow-up		72		87		80
EFS at 14 years of follow-up		67		74		68

ABVD/MOPP (arm A) and 112 to ABVD/OPP (arm B). The median follow-up is 111 months (range 12-167) in arm A and 98 months (range 12-167) in arm B. In arm A, the median age was 31 years, 57% of patients were males and 76% had stage IIIB/IV disease. In arm B the median age was 31 years, 57% of patients were males and 71% had stage IIIB/IV disease. Results of treatment are show in Table 2. The rate of CR for the entire group was 90%. The corresponding figure was 92% in the ABVD/MOPP group and 88% in the ABVD/OPP group. Fifty-three percent of patients are alive in first continuous CR (CCR) (47%, range 63-167 months for arm A, and 58%, range 67-167 months for arm B). The median number of cycles required to achieve CR was 4. Nine patients failed the MOPP/ABVD regimen, with 8 of them dying of HD and 1 remaining alive with disease. In the ABVD/OPP arm, 13 patients failed treatment: 11 of them died of HD and 2 are still living in CR after a second line treatment. The CR rate of the total group of patients was not adversely affected by any of the factors considered for the statistical analysis.

The 14-year OS, RFS, EFS rate in arm A was 72%, 72%, 67%, and in arm B 82%, 87%, 74%, respectively (Figures 1, 2, 3). No differences were observed between the two arms, except for patients with stage IIIB treated with ABVD/MOPP who showed a RFS of 78%, compared with 92.5% for the ABVD/OPP group; this difference, however, was not statistically significant ($p > 0.05$).

Of all patients who achieved CR, 35 (16%) relapsed. In the ABVD/MOPP arm, 20 patients (20%) relapsed after a median of 18 months (range 2-136); twelve patients of this group did not achieve a second CR and died of HD; eight patients (40%) achieved a second CR. Of these 8 patients, 1 developed a secondary acute myeloid leukemia (AML) and died after a third-line chemotherapy regimen, 2 patients relapsed and are still alive with disease and 5 patients are still alive in second CR. In the ABVD/OPP arm, 15 patients (15%) relapsed after a median of 23 months (range 3-59); five patients of this group did not

Table 3. Toxicity.

	MOPP/ABVD		OPP/ABVD		
	no.	%	no.	%	
Acute toxicity					
No. of patients evaluable	106		112		
Hematologic (grade of toxicity > 2)*	58	55	35	31	$p < 0.01$
Neurologic (grade of toxicity > 2)*	1	1	2	2	
Gastrointestinal (grade of toxicity > 2)*	5	5	5	4	
Cardiac	0	0	1	1	
Viral infection (herpes zoster)	2	2	4	3	
Chronic toxicity					
Lung (fibrosis)	4	4	6	5	
Viral infection (herpes zoster)	24	22	29	26	
Cardiac	8	7.5	9	8	
Thyroid	4	4	2	2	
Aseptic necrosis	2	2	1	1	
Secondary neoplasm	6	6	2	2	$p > 0.1$
Non Hodgkin's lymphoma	2	2	0	0	
Leukemia	2	2	2	2	
Solid tumors	2	2	0	0	

*According to WHO criteria.

achieve a second CR and died of HD, 10 patients (66%) achieved a second CR: 1 died of interstitial pneumonia after autologous bone marrow transplantation, 1 died of myocardial dilatative disease and 8 are still alive in second CR.

Of the 106 patients in arm A, 28 (26%) died. The causes of death were the following: 20 patients died of HD, 5 developed a secondary neoplasm (2 NHL, 2 AML, 1 lung cancer), 3 patients died during CR (1 sepsis, 1 interstitial pneumonia, 1 cerebral hemorrhage).

Of the 112 patients in arm B, 19 (17%) died. Fourteen died of HD, 2 developed a secondary neoplasm (2 AML) and 3 died in CR (1 myocardial dilatative disease, 1 interstitial pneumonia, 1 myocardial infarct). In the 14-year follow-up, the analysis of total relapses revealed that 40% of patients who relapsed after ABVD/MOPP achieved a second CR with a salvage chemotherapy, compared with 66% for patients who relapsed after ABVD/OPP. This difference was statistically significant ($p < 0.001$).

Toxicity

Toxicity was evaluated according to the WHO criteria.¹⁴ In the MOPP/ABVD arm, acute hematologic toxicity (> grade 2) was significantly higher than in the OPP/ABVD arm ($p < 0.01$). No differences were observed between the two arms with regard to gastrointestinal toxicity. Acute cardiac toxicity in the ABVD/OPP group also included a case of fatal myocardial infarction in a 60-year-old patient occurring immediately after the end of chemotherapy (Table 3).

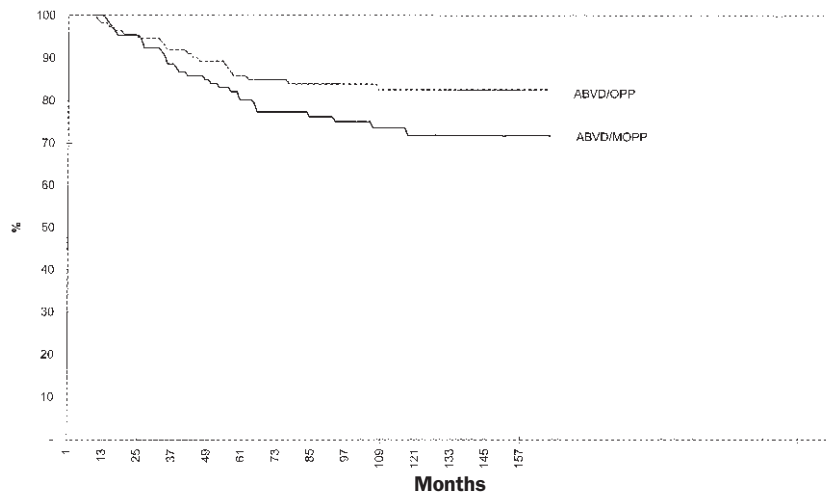


Figure 1. Survival ABVD/MOPP + ABVD/OPP.

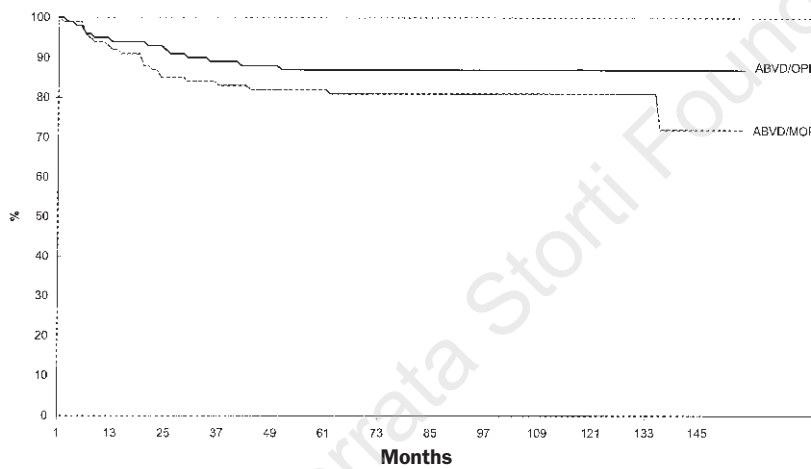


Figure 2. RFS ABVD/MOPP + ABVD/OPP.

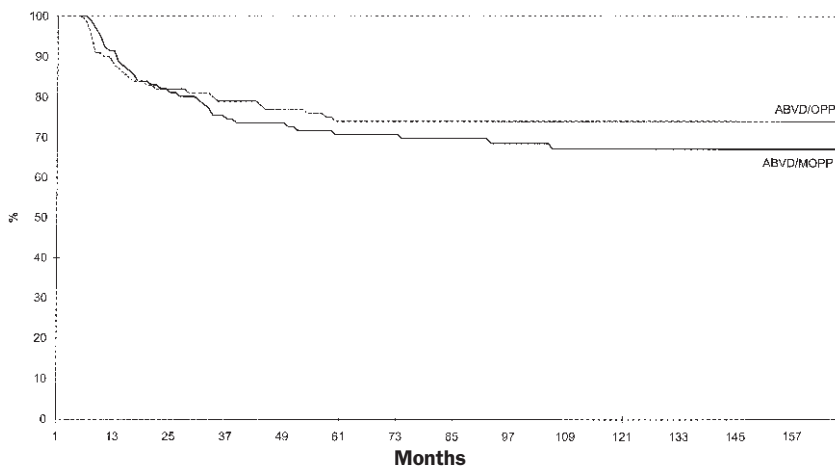


Figure 3. EFS ABVD/MOPP + ABVD/OPP.

Chronic toxicity occurred in the ABVD/MOPP group, there being 2 cases of avascular necrosis. Six secondary tumors occurred in the ABVD/MOPP arm (2 NHL, 2 AML, 1 lung cancer, 1 breast cancer) and 2 AML in the ABVD/OPP arm.

Finally, 11 patients, 5 in the ABVD/MOPP arm and 6 in the ABVD/OPP arm, developed respiratory complications characterized by lung para-mediastinal fibrosis with persistent reduction of the vital capacity (Table 3).

Gonadal toxicity was evaluated by semen analysis in men and by menses evaluation in women; hormonal tests and sexual function assessment were conducted as previously reported.^{17,18} Thirty males were evaluable in each group; thirty one women in arm A and 27 in arm B were evaluable. No significant differences in azoospermia (76% vs 73%) and persistent amenorrhea (48% vs 63%) were observed in arms A and B, respectively.

Conclusions

Although the use of combination chemotherapy is well established in the management of advanced stage HD the question whether an eight-drug regimen is more effective than a four-drug regimen still remains unresolved.¹⁹ The superiority of alternating ABVD/MOPP over MOPP alone was initially reported in the Milan study, performed in patients with stage IV disease with a significant advantage for the eight-drug regimen with a RFS and EFS of 73% and 65%, compared to 50% and 45% with the four-drug regimen.³ Although in the CALGB trial alternating ABVD/MOPP yielded significantly superior rates of CR and EFS compared to MOPP alone (83% vs 62% and 66% vs 47% respectively), in this study no differences were observed between ABVD/MOPP and another four drug-regimen such as ABVD.²⁰ Moreover, two other studies showed no significant CR, RFS, EFS advantage of eight-drug combinations in comparison with the MOPP regimen: the NCI combination MOPP/CABS vs MOPP alone and the *Southeastern Cancer Study Group* comparing BCVPP-bleo vs BCVPP-bleo alternating with doxorubicin, dacarbazine and bleomycin.^{21,22}

In the present study, we observed that with 8 courses of ABVD/MOPP vs hybrid ABVD/OPP with the addition of an involved field radiotherapy (20 Gy) it was possible to obtain a high complete remission rate with a low risk of relapse and an acceptable toxicity. No significant differences between the two regimens were observed, with 91% CR for group A patients and 88% for group B patients and 70% and 74% of patients alive in CCR, respectively. The actual RFS at fourteen years was 72% for arm A and 87% for arm B ($p > 0.5$), and the OS 72% and 82% respectively.

The acute and long-term toxicity of this program was moderate.

In arm A, 20 patients died of HD. The other causes of death included NHL (2 patients), AML (2 patients), pulmonary failure (1 patient), sepsis (1

patient), cerebral hemorrhage (1 patient), lung cancer (1 patient). In arm B, 14 patients died of HD. The other causes of death included: myocardial infarct (1 patient), myocardial dilatative disease (1 patient), AML (2 patients), pulmonary failure (1 patient).

In the ABVD/OPP arm, hematologic tolerance was better than in the ABVD/MOPP arm; there were fewer secondary neoplasms (2 vs 6), but this difference was not significant; patients who relapsed achieved a second CR more frequently than in the MOPP/ABVD arm and this difference proved statistically significant. No patients relapsed after 5 years of CR in ABVD/OPP arm and 1 patient relapsed after 13 years of CR in the ABVD/MOPP arm. Thus, both hybrid schemes of chemotherapy followed by radiotherapy produce a high percentage of CR, a low risk of relapse and an acceptable toxicity.

These results can be considered satisfactory if one takes into account the patients with advanced and symptomatic disease entered in this study. One of the end points of the study was thus achieved: the ABVD/OPP scheme resulted as effective as the well known ABVD/MOPP scheme but with a lower hematological toxicity (this difference was statistically significant), less secondary tumors (this difference was not statistically significant) and a greater likelihood of obtaining a second CR (this difference was statistically significant).

Contributions and Acknowledgments

APA was responsible for the conception of the study, formulated the study design, took part in assessment of patients and wrote the paper. EC carried out data analysis. RME, VD and EP were involved in clinical assessment of patients. CB and FM gave final approval of the version to be published. All the authors contributed to the execution of the study and writing of the paper.

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Disclosures

Conflict of interest: none.

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