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MOPPEBVCAD Chemotherapy with Limited and Conditioned Radiotherapy in Advanced Hodgkin's Lymphoma: 10-Year Results, Late Toxicity, and Second Tumors

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Abstract

Purpose: MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) chemotherapy with limited radiotherapy was devised in 1987 to reduce late toxicity and second tumor incidence while trying to improve effectiveness through increases of dose intensity and dose density. Late results, toxicity, and second tumor incidence were reviewed in all the patients treated.

Experimental Design: The drugs of three previous alternating regimens [CAD (lomustine, melphalan, and vindesine), MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), and ABV (doxorubicin, bleomycin, and vinblastine)] were intensified and hybridized, the cumulative dose of mechlorethamine was lowered, and irradiation was delivered to no more than two sites either bulky or partially responding to chemotherapy.

Results: A total of 307 previously untreated advanced-stage patients underwent MOPPEBVCAD chemotherapy. Radiotherapy was delivered to 118 of 307 patients (38%). Remission was complete in 290 patients (94%). With a median follow-up of 114 months, 10-year overall, disease-free, and failure-free survival rates were 79%, 84%, and 71%, respectively. Forty-two patients relapsed and 60 died. The causes of death were Hodgkin's lymphoma in 36 patients, second neoplasms in 12, cardiorespiratory diseases in 4, pulmonary diseases in 2, and unknown in 6. Sixteen second tumors (of which nine were myelodysplasia and/or acute leukemia) were diagnosed in all. Outside this series of 307 patients, MOPPEBVCAD obtained complete responses in 12 of 15 relapsed and 9 of 9 refractory patients who had previously been treated with other regimens.

Conclusions: Clinical response and long-term results are very satisfactory, whereas the second tumor incidence was lower than would have been expected with MOPP analogues. Given its response/late toxicity balance, MOPPEBVCAD does not undermine the leading role of ABVD as first-line regimen but can be indicated as a very effective second-line conventional therapy.

In the last few decades, Hodgkin's lymphoma has passed from being a fatal disease to being one of the most curable human cancers. However, despite this clinical progress, 20% to 30% of patients progress or relapse. Furthermore, long-term survivors are still at risk of late treatment–related complications, such as cardiac or pulmonary dysfunction, infertility, thyroid-related sequelae, or second tumors. The malignancies most frequently associated with chemotherapy include acute myeloid leukemia and myelodysplastic syndrome (AML/MDS), whereas the use of radiation therapy is related to a constantly increasing risk of second solid tumors.

The standard chemotherapy combination for advanced Hodgkin's disease was MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) in the 1970s and 1980s and for the last 15 years has been ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). A mathematical model devised by Goldie and Coldman (1) relating the drug sensitivity of tumor cells to the spontaneous mutation rate of cells led many

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investigators, particularly between 1980 and 1990, to design new chemotherapy schedules that either alternated some of the most effective regimens in use [i.e., MOPP/ABVD (2), MOPP/CABS (CCNU, doxorubicin, bleomycin, and streptozocin) (3), MOP-BAP (bleomycin, doxorubicin, and procarbazine) (4), MOPP-CAVmP (cyclophosphamide, doxorubicin, teniposide, and metilprednisolone) (5), and BCVPP (BCNU, vinblastine, cyclophosphamide, procarbazine, and prednisone)/ABD (doxorubicin, bleomycin, and decarbazine) (6)] or hybridized them by delivering in each cycle all the drugs scheduled in different regimens [MOPP/ABV (7), MA/MA (MOPP on day 1, ABVD on day 15 of each monthly cycle) (8), ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone)/EVA (etoposide, vincristine, and doxorubicin) (9)]. More recently, a statistical model by the German Hodgkin Study Group, which considers tumor growth and chemotherapy effects (10), indicated that intensifying drug doses through considerable dose escalation could be the best choice: The result of this theory was the BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) schedule (11, 12).

However, in 1987, in agreement with the then contemporary, evolving basic criteria of chemotherapy for advanced Hodgkin's lymphoma, the Italian Lymphoma Study Group [Gruppo Italiano per lo Studio dei Linfomi (GISL)] designed a shortened, hybridized, and intensified version of Straus' alternating regimen, CAD/MOPP/ABV (13), and combined it with a restricted use of radiotherapy, which was limited to sites of bulky involvement or to areas that had not responded completely to chemotherapy. The basic idea underlying the formulation of the MOPPEBVCAD regimen was to improve an already existing treatment program, widely tested and highly effective, by introducing selected chances. The hybridization of the drugs of alternating CAD/MOPP/ABV into the MOPPEBVCAD schedule complied more closely with Goldie and Coldman's (1) theory. Moreover, the adopted modification of the original schedule seemed to partially accomplish the improvements indicated by Norton and Simon's (14) model, at least as far as the dose density was concerned. The contemporary increase of dose intensity and dose density was obtained for the majority of drugs by administering in six cycles approximately the same cumulative drug dosage delivered with the original nine cycles of the alternating CAD/MOPP/ABV and by reducing the cycle length from 35 to 28 days. The total dose of mechlorethamine was reduced by 50%. The delivery of radiotherapy was limited and conditioned to the presence of no more than two areas with either an original bulky mass and/or a lesion incompletely remitting after chemotherapy.

The early data on feasibility, toxicity, and short-term results of this modified chemotherapy program, collected in different trials, were encouraging (15–18). We report here the cumulative experience—with particular attention to late results and toxicity—achieved in all the patients evaluated in those original studies.

Patients and Methods

Patients. In this study, we reviewed and updated the clinical information regarding all those patients treated with MOPPEBVCAD chemotherapy plus limited radiotherapy who were enrolled and considered eligible in the three distinct clinical trials that administered this combined therapy in at least one treatment arm. The population of the present study, therefore, comprised the 145 patients enrolled in a controlled, open, nonrandomized study carried out by the GISL (15, 16) between 1988 and 1993, together with 24 patients evaluated in a prior, unpublished pilot study carried out during 1987, the 32 patients randomized to MOPPEBVCAD—with or without radiotherapy—in a second GISL study (17) conducted from 1994 to 1995, and, finally, the 106 subjects randomized to the same treatment in a randomized trial of the Intergruppo Italiano Linfomi (18) between 1996 and 1999. In the second GISL study (17), the MOPPEBVCAD regimen was compared against a variant in which cyclophosphamide substituted lomustine and etoposide substituted melphalan (MOPPEBVCyED). In the Intergruppo Italiano Linfomi trial (18), patients were randomized into three different treatment arms—MOPPEBVCAD, ABVD, and Stanford V chemotherapy. In all these studies, the criteria adopted for administration of radiation therapy did not differ.

Enrollment requirements, staging procedures, and treatment criteria were the same in the three trials and were detailed in each study report. Synthetically, unequivocal histology of Hodgkin's lymphoma, age between 15 years and an upper limit varying from 65 to 75 years according to the trial, no previous treatment and clinical stage IIB, III, or IV were necessary for entry to the study. Staging was evaluated according to the recommendations of the Cotswolds Meeting (19); in particular, all patients underwent computed tomography of the thorax, abdomen, and pelvis and had a bone marrow core biopsy taken from one iliac spine only.

A total of 307 patients (enrolled from 1988 to 1999) were eligible for the evaluation presented here. The clinical characteristics of these patients are listed in Table 1.

Chemotherapy. The drug doses and time schedule of the MOPPEBVCAD hybrid regimen are listed in Table 2. Six cycles of chemotherapy were planned. Growth factors were not available before 1992 in Italy and after that time were not permitted routinely, but used only in cases of severe neutropenia ($< 0.5 \times 10^9$/L) associated with fever or other signs of infection. When growth factors were necessary, they were administered in the shortest period included in the restricted time interval from day 16 to 25 of the whole regimen.

In potentially fertile young women who did not have specific contraindications, ovulation was suppressed throughout the treatment with third-generation progestins (desogestrel and gestodene) or with triphasic estrogen-progestin combinations.

Radiotherapy. This was not routinely associated with chemotherapy but was administered only to patients who presented bulky masses (according to the Cotswolds Meeting criteria) at their staging evaluation or had involved sites that showed only partial response after chemotherapy. Treatment with radiotherapy was possible only on condition that no more than two lymph node areas fulfilled the above requirements. This led to a minority of patients in each clinical trial undergoing radiation therapy, precisely 32% (15, 16), 37% (17), and 47% (18) in the three trials, respectively, corresponding to an average 38% of the whole series of 307 cases. Radiotherapy had to start 4 to 6 weeks after the end of chemotherapy. The recommended total doses were 36 Gy to areas with no signs of disease at the end of chemotherapy [cases with bulky masses in complete remission (CR) or unconfirmed remission] and 42 Gy to sites with partially persisting disease. Volumes of radiotherapy as well as technical equipment were possibly different in the distinct radiotherapy units involved in the trials.

Assessment of response and statistical analysis. Residual lesions after treatment were evaluated by ^{67}Ga scintigraphy and computed tomography, and, more recently, through positron emission tomography. CR was defined as complete regression of measured lesions and disappearance of the other objective signs and symptoms of lymphoma for at least 3 months. Partial remission corresponded to a decrease of >50% in the sum of the products of the diameters of the measurable lesions with disappearance of any symptom. Progressive disease was defined as a ≥25% increase in the size of at least one measurable lesion, or the appearance of a new lesion or recurrence of constitutional

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Table 1. Clinical characteristics of the patients at diagnosis

	GISL			IIL	Total
	Pilot	Nonrandomized	Randomized	Randomized	
	1987	1988-1993	1994-1995	1996-1999	1987-1999
Patient no.	24	145	32	106	307
Male/female	11/13	85/60	15/17	55/51	166/141
Age (y), median (range)	29 (17-59)	35 (16-75)	33 (16-69)	34 (15-65)	34 (16-75)
Histology*					
LP	0	1	1	7	9
NS	17	88	21	66	192
MC	2	42	8	26	78
LD	1	12	1	2	16
Unclassified	4	2	1	5	12
Stage*					
IIB	6	45	9	26	86
IIIA	7	22	5	23	57
IIIB	2	39	6	32	79
IVA	8	11	6	11	36
IVB	1	28	6	14	49
Karnofsky index, median (range)	80 (40-100)	80 (50-100)	80 (60-100)	80 (50-100)	80 (40-100)
Bulky disease*	4	47	5	19	75
Bone marrow involvement	4	22	4	12	40
Hemoglobin (g/L), m ± SD	102 ± 22	119 ± 20	114 ± 18	107 ± 19	113 ± 20
Serum LDH (units/L), m ± SD	586 ± 266	400 ± 225	352 ± 185	515 ± 196	449 ± 192
Serum albumin (g/L), m ± SD	30.5 ± 8.2	36.4 ± 5.9	39.0 ± 6.1	32.3 ± 7.1	34.8 ± 6.8
ESR (mm/1st h), median (range)	66 (8-148)	62 (7-133)	59 (5-113)	56 (7-121)	60 (5-140)
WBC (10^9/L), m ± SD	13.4 ± 9.1	11.3 ± 7.9	13.6 ± 10.8	13.4 ± 8.6	12.5 ± 9.3

Abbreviations: IIL, Intergruppo Italiano Linfomi; LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; m ± SD, arithmetic mean ± 1 SD; ESR, electron spin resonance.
*$P < 0.0500$ for the distribution of the characteristic among the four groups, χ^2 test.

symptoms. No response was variation of the measurable lesions ranging from that of partial remission to that of progressive disease.

Toxicity was measured according to standard Eastern Cooperative Oncology Group criteria (20).

Dose intensity was calculated according to the criteria reported by Hryniuk (21) and examples and suggestions offered by De Vita et al. (22).

Overall survival was determined from the date of diagnosis to the date of last observation or death (from any cause). Disease-free survival for complete responders was measured from the date of therapy completion to the date of last observation or relapse. Failure-free survival was computed from the start of treatment to one of the following events: death from disease or treatment, disease progression, or relapse. Survival curves were calculated on a intention-to-treat basis using the method of Kaplan and Meier (23, 24). Standard χ^2 test and ANOVA (25) were used to evaluate the distribution of clinical characters, biochemical values, response variables, and toxicity grades among the groups of patients of each original trial.

Results

A total of 1,751 cycles of MOPPEBVCAD were administered in 307 patients (mean number of cycles per patient: 5.6, range 3-8) with a 0.73 ± 0.12 mean relative dose intensity, which showed minimal variations among the four distinct multicenter studies as detailed in Table 3 (0.72 ± 0.11, 0.75 ± 0.13, and 0.73 ± 0.14).

Although complete information on the acute toxicity was given in the original trial reports (15–18), we should emphasize that hematologic toxicity, mainly neutropenia and thrombocytopenia, was the major factor that limited the dose intensity actually administered (Table 4). Seventy-four subjects (24%) received granulocyte colony-stimulating factor for at least a few days and the cumulative dose intensity of

Table 2. Drug doses and time schedule of MOPPEBVCAD regimen

Drugs	mg/m²	Route	Days
Mechlorethamine	6	i.v.	1 (cycles 1, 3, and 5, only)
Lomustine	100	oral	1 (cycles 2, 4, and 6, only)
Vindesine	3	i.v.	1
Melphalan	6	oral	1-3
Prednisone	40	oral	1-14
Epidoxorubicin	40	i.v.	8
Vincristine	1.4	i.v.	8
Procarbazine	100	oral	8-14
Vinblastine	6	i.v.	15
Bleomycin	10	i.v.	15

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Table 3. Parameters of therapy and clinical outcome

Study	GISL			IIL	
	Pilot (1987)	Nonrandomized (1988-1993)	Randomized (1994-1995)	Randomized (1996-1999)	Total (1987-1999)
No. patients	24	145	32	106	307
No. cycles	119	844	179	609	1,751
Mean (range)	5.0 (3-6)	5.8 (3-8)	5.6 (3-6)	5.7 (4-6)	5.6 (3-8)
Cumulative DI, mean ± SD	0.77 ± 0.15	0.72 ± 0.11	0.75 ± 0.13	0.73 ± 0.14	0.73 ± 0.12
Response to CT					
CR	18	112	26	82	238
PR	6	29	5	24	64
NR	0	4	1	0	5
RT	8/24	47/145	13/32	50/106	118/307
Interval CT-RT (d), mean (range)	31 (20-42)	33 (22-47)	33 (23-42)	42 (24-48)	36 (20-48)
Response to CT (+RT)					
CR	21	137	32	100	290
PR	2	4	0	6	12
NR	1	4	0	0	5

Abbreviations: DI, dose intensity; CT, chemotherapy; RT, radiotherapy; PR, partial remission; NR, null response.

chemotherapy in these patients was slightly lower than that in patients who did not require growth factors (0.72 ± 0.09 versus 0.74 ± 0.11). Nonhematologic toxicity was acceptable and generally well controlled. In particular, neurotoxicity was relatively frequent but was fully tolerable in spite of the three distinct *Vinca* derivatives included in the schedule.

Table 3 reports the clinical outcome besides some therapeutic details. Response after chemotherapy was complete in 238 patients (78%), partial in 64 (21%), and null in 5 (2%). Radiotherapy was administered to 118 patients (38%), 64 of whom had at least one partially remitting lesion. The mean interval between the end of chemotherapy and the start of radiotherapy was 5 weeks. Radiation doses ranged from 26 to 44 Gy (mean ± SD: 37.3 ± 5.6).

After chemotherapy and radiotherapy, when delivered, 290 patients achieved CR (94%), 12 obtained only partial remission (4%), and the remaining 5 did not respond at all (2%). Forty-two patients of the 290 complete responders relapsed at variable intervals after the cessation of therapy (from 3 to 104 months). Fifteen of them underwent high-dose chemotherapy followed by peripheral blood stem cell transplantation (nine patients achieved a CR, four a partial remission, and two had no response); six further patients were rescued to CR by means of extended radiotherapy programs; the remaining 21 cases were treated with other chemotherapy regimens and only four of them reached a second CR.

Thus far, 60 patients have died. The causes of death were Hodgkin's disease in 36 patients (early treatment-related death, progression after either first-line chemotherapy failure, or one or more relapses), a second neoplasm in 12, cardiorespiratory disease in 4, pulmonary disease in 2, and unknown in 6. In particular, among the fatal, acute, treatment-related adverse effects, there was one case of progressive multifocal leucoencephalopathy, one of fatal gastric hemorrhage during serious pancytopenia, and one sudden cardiac death.

With a median follow-up of 114 months (range 20-197), 10-year overall, disease-free, and failure-free survival rates were 79%, 84%, and 76%, respectively (Fig. 1).

With regard to second neoplasms, nine patients (2.9%) developed a secondary AML/MDS. Five of them were treated with MOPPEBVCAD only, four also with combined radiotherapy, and two of these last had additional chemotherapy for relapse. Solid tumors were recorded in four patients

Table 4. Percentages of grades 3 and 4 acute toxicity in the 307 patients

Study	ECOG grades 3/4				
	GISL			IIL	Total
	1987	1988-1993	1994-1995	1996-1999	1987-1999
Patients	24	145	32	106	307
Hemoglobin	4/1	10/4	6/1	16/4	36/10
Leukocyte count	13/6	36/17	12/8	37/17	98/48
Neutrophil count	10/5	38/21	10/6	38/16	96/48
Platelet count	6/0	29/17	5/4	16/9	56/30
Nausea/vomiting	2/0	14/0	0/1	5/2	21/3
Alopecia	2/0	15/0	1/0	2/0	20/0
Neurologic toxicity	1/0	7/0	0/1	7/2	15/3
Mucositis	1/0	0/0	2/0	1/0	4/0

NOTE: Differences in the distribution of the grades of toxicity among the four groups are not statistically significant.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

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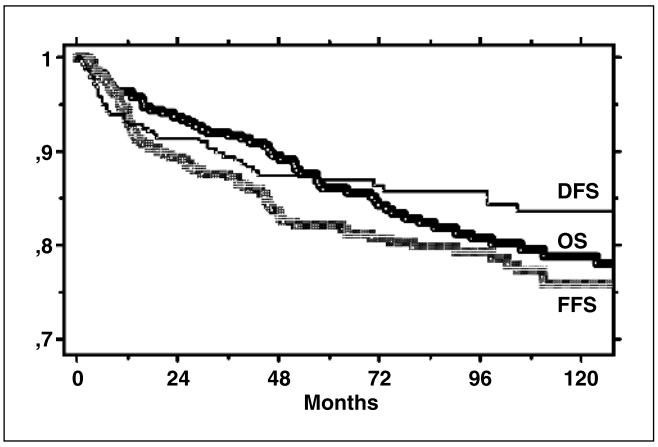

Fig. 1. Kaplan-Meier analysis of the probability of overall survival (*OS*), disease-free survival (*DFS*), and failure-free survival (*FFS*).

(1.3%): three cases of lung carcinoma (one was synchronous, the other two developed in patients who also had received radiotherapy) and one colorectal cancer in a subject treated with chemotherapy only. A second non-Hodgkin's lymphoma was observed in three patients (1%), all of whom had also received radiotherapy. On the whole, 9 of 16 second tumors arose in patients who had undergone combined chemotherapy and radiotherapy and only in two of these nine cases after an additional second-line chemotherapy. The median interval between the end of initial therapy for Hodgkin's lymphoma and diagnosis of secondary AML/MDS was 22.4 months (range: 8-132 months). Six of the nine cases of secondary AML or MDS occurred within 5 years from completion of the initial therapy. The median survival after the diagnosis of AML/MDS was 10 months (range: 8-36).

One patient developed essential thrombocytopenia 4 years after treatment and two complained of hypothyroidism (both were irradiated after chemotherapy and are presently taking hormone replacement therapy).

Fertility was not specifically studied in these high-risk patients, but was informally assessed during the routine follow-up of the patients. However, of the 26 women who were in the fertile age (15-45 years), were sexually active, and did not continue contraceptive use after the end of treatment, five normal pregnancies were recorded 2, 3, 10, 11, and 14 years after treatment; two men were also recorded to have fathered children.

Besides being used as front-line therapy, MOPPEBVCAD was used as a salvage regimen in 24 patients outside the 307 of this evaluation. Most of these subjects had early-stage disease and did not undergo high-dose chemotherapy plus peripheral blood stem cell transplantation because of various comorbid conditions or older age. Nine of these 24 patients had refractory disease (two after VBM + radiotherapy, four after CVPP + radiotherapy, and three after ABVD or EVE + radiotherapy), whereas 15 had relapsed (5 within and 10 beyond 12 months from the end of treatment, which had been VBM + radiotherapy in three cases, CVPP + radiotherapy in three and ABVD or alternating MOPP/ABVD in nine). Clinical response to this second-line MOPPEBVCAD therapy was complete in 21 patients (nine of nine refractory ones), partial in one, and null in two. The clinical results in this particular setting were only slightly inferior to those recorded in the corresponding patients in the same trials who underwent high-dose chemotherapy followed by transplantation procedures.

Discussion

The clinical response to MOPPEBVCAD plus limited and conditioned radiotherapy (94% CR rate) was similar or even better than that achieved with the best and most recent chemotherapy regimens. The CR rate obtained by MOPP/ABV hybrid ranges from 80% (26, 27) to 83% (28), by standard BEACOPP 88% (11), by escalated BEACOPP 96% (12), by COPPABVD 85% (12), and by COPP/ABV/IMEP 77% (29).

These results seem to give credit to Goldie and Coldman's theory that underlies the strategies of hybridization and intensification in which the drug doses of the alternating nine cycles of CAD/MOPP/ABV were condensed and redistributed in six cycles of MOPPEBVCAD. The actually administered 0.73 average, relative dose intensity, with respect to the planned doses and time length of MOPPEBVCAD, correspond to a 1.12 intensification of the truly delivered doses in the original alternating schedule. This intensification is probably the main cause of the remarkable improvement in response with respect to the original alternated CAD/MOPP/ABVD (78% CR rate; ref. 13), although we must consider also the parallel 50% increase of dose density produced by our modification. The new regimen was found to be particularly effective despite the decidedly reduced radiotherapy program optionally combined with the chemotherapy. Moreover, the regimen was always administered in different multicenter settings, which testifies to its feasibility and gives assurance of the reproducibility of the results.

A comment is needed on the early and late toxicity related to MOPPEBVCAD chemotherapy.

Early hematologic toxicity was remarkable but manageable. About 32% of the patients completed the combined therapy before growth factors were available in Italy; thereafter, they were used, strictly on demand, in 24% of the patients treated after 1992 when growth factors did become available. The acute nonhematologic toxicity can be considered fully acceptable; in particular, the administration of the three different *Vinca* alkaloids incorporated in the schedule did not seem to cause a significant price in terms of neurotoxicity.

Treatment-related mortality was low in absolute terms and lower than that of the majority of the regimens tested for advanced Hodgkin's lymphoma (Table 5).

When designing MOPPEBVCAD, there was great concern about the potential oncogenic effect of the three different alkylating agents and one nitrosurea present in the schedule. To reduce the risk of second tumors without lowering effectiveness, the total dose of mechlorethamine was reduced by 50% compared with that delivered in the original chemotherapy program and, moreover, both the extension and doses of radiotherapy were strongly limited. The number of second cancers actually observed (2.9% AML/MDS, 2.3% solid tumors) was higher than we expected from such modifications but can be considered lower than that recorded after many other chemotherapy regimens for advanced Hodgkin's lymphoma (30). The hitherto published very large, retrospective studies of patients pooled from differently treated series are not suitable for making reliable comparisons of the risk of the regimens

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Table 5. Results of the main alternating or hybrid regimens in the treatment of advanced Hodgkin's disease recorded in the last 15 years

Authors	CT	No. patients	CR (%)	OS (%)	DFS (%)	FFS (%)	TRM (%)	AML (%)	SST (%)	Median follow-up (mo)
Connors et al. (32)	MOPP/ABV hybrid	153	80	81 (5 y)	NG	71 (5 y)	3	NG	NG	60
	MOPP/ABVD alternating	148	76	83 (5 y)	NG	67 (5 y)	1	NG	NG	60
Glick et al. (27)	MOPP/ABVD alternating	344	75	71 (8 y)	NG	54 (8 y)	NG	2.6	NG	88
	MOPP/ABVD hybrid	347	83	79 (8 y)	NG	64 (8 y)	NG	0.3	NG	88
Radford et al. (26)	ChlVPP/EVA	144	62	89 (5 y)	78 (5 y)	NG	3	0.7	2.7	59
	VAPEC-B	138	47	79 (5 y)	58 (5 y)	NG	1. 5	0	2.2	59
Horning et al. (28)	Stanford V	142	NG	96 (5 y)	NG	89 (5 y)	0	0	0.7	65
Canellos et al. (33)	MOPP	123	NG	59 (5 y)	NG	40 (10 y)	NG	NG	NG	169
	ABVD	115	NG	66 (10 y)	NG	59 (10 y)	NG	NG	NG	169
	MOPP/ABVD alternating	123	NG	64 (10 y)	NG	52 (10 y)	NG	NG	NG	169
Diehl et al. (12)	BEACOPP standard	469	88	88 (5 y)	76 (5 y)	NG	<2	0.6	2.1	54
	BEACOPP, escalated	466	96	91 (5 y)	87 (5 y)	NG	<2	2.5	2.6	51
	COPP/ABVD	260	85	83 (5 y)	69 (5 y)	NG	<2	0.4	2.7	72
Duggan et al. (34)	ABVD	433	76	82 (5 y)	NG	63 (5 y)	2.1	0.47	3.7	60
	MOPP/ABV hybrid	419	80	81 (5 y)	NG	66 (5 y)	3.6	2.6	4.0	60
Sieber et al. (29)	COPP/ABV/IMEP hybrid	293	77	73 (7 y)	NG	54 (7 y)	2.74	0.68	2.04	84
	COPP/ABVD	291	78	73 (7 y)	NG	56 (7 y)	3.07	2.06	1.03	84
Martinelli et al. (35)	ChlVPP/ABVVP hybrid	61	95	79 (5 y)	81 (5 y)	72 (5 y)	0	1.6	NG	60
Present series	MOPPEBVCAD	307	94	74 (10 y)	80 (10 y)	78 (10 y)	0.98	2.9	2.3	114

Abbreviations: OS, overall survival; DFS, disease-free survival; FFS, failure-free survival; TRM, treatment-related mortality; SST, solid second tumors; NG, not given.

causing second cancer. In Table 5, we have listed only those randomized trials with a sufficiently long follow-up to offer a clear-cut incidence per treatment arm and able to show the relationship between a single treatment and the second cancers that arise after it.

From this point of view, the 2.9% incidence of second AML/MDS recorded at 10 years following MOPPEBVCAD is a true reduction with respect to incidences recorded after 5 or 6 years with many other regimens (30). Moreover, the cumulative 10-year incidence of AML/MDS is probably a definitive estimate because the incidence does not tend to increase beyond 10 to 12 years after the end of treatments (30). Similarly, the 10-year cumulative incidence of second solid tumors after MOPPEBVCAD (2.3%) is comparable with the percentages recorded at 5 to 6 years following the majority of the other multiple drug regimens. In such comparisons, the relatively high proportion of mature and elderly patients in our series (20% >50 years of age) must be considered because this proportion is higher than that of most of the patient populations listed in Table 4. As it is well known, age >45 years at diagnosis is an unfavorable prognostic factor in Hodgkin's lymphoma (31).

With the aim of minimizing the oncogenic potential of MOPPEBVCAD, some modifications of this schedule have already been tested and others are under evaluation. Probably, the type of drugs included in the therapeutic combinations also plays a crucial but not quantified role in these models, besides that undeniable of drug dose size, intensity, or density. We are not referring to the intensive and frequent use of *Vinca* alkaloids in the MOPPEBVCAD, which includes vindesine, vincristine, and vinblastine in weekly sequence in each cycle, but to the proven role of even low doses of lomustine and melphalan. A brief randomized trial by GISL, published in 2000 (17), tested a possibly less toxic variant of MOPPEBVCAD, MOPPEBVCyED, in which cyclophosphamide and etoposide replaced lomustine and melphalan, respectively, whereas all the other drugs were the same. This modified regimen actually showed lower early toxicity, and the study was closed after the planned number of patients had been treated. However, in the subsequent years of follow-up, it was associated with a higher failure rate and with a difference that approached the conventional levels of statistical significance. The conclusion was that lomustine and melphalan are decisive in the efficacy of the combination; thus, that trial did not contribute to reducing the risk of second cancers but simply added evidence of the effectiveness of two drugs in the schedule. A subsequent GISL trial, started at the end of 2000 and still ongoing, is evaluating a new modification of the schedule in which mechlorethamine is replaced by cyclophosphamide while all other drugs and doses are unmodified. The interim analyses can currently only testify to the excellent effectiveness of the regimen, obviously providing no information on its oncogenicity. In the near future, positron emission tomography–aided evaluation of the response after chemotherapy might further restrict the criteria for the use of radiotherapy after MOPPEBVCAD. Moreover, in the case of radiotherapy, volumes of radiotherapy must be made homogeneous; doses ranging from 30 to 36 Gy seem to be most suitable.

In conclusion, our experience with MOPPEBVAD with limited radiotherapy can be summarized as follows:

- MOPPEBVCAD ± radiotherapy produces excellent clinical responses in patients with advanced Hodgkin's

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lymphoma and, at present, can be considered among the group of combination treatments with absolutely the best clinical performance.

- Nearly half of the patients who relapsed can be further rescued with high-dose chemotherapies followed by bone marrow transplantation (better) or with conventional treatments (less good).
- Treatment-related mortality is near the lower range observed with most of the intensive regimens for advanced Hodgkin's lymphoma, and early toxicity, mainly hematologic, is considerable but manageable.
- Overall, failure-free and progression-free survival curves at 10 years are among the best recorded with conventional treatments.
- The 10-year incidence of second cancers is considerably reduced if compared with that following analogous treatments with similar follow-up; however, it is still higher than that following ABVD.
- The effectiveness/second cancer ratio is slightly in favor of the ABVD regimen, which must still be considered the gold standard; nevertheless, MOPPEBVCAD represents a very good second-line regimen for patients who are not candidates for high-dose chemotherapy.

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