



Lomustine and melphalan cannot be replaced by cyclophosphamide and etoposide without reducing efficacy in MOPPEBVCAD chemotherapy for advanced Hodgkin's disease

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ABSTRACT

Background and Objectives. To evaluate the feasibility, toxicity and preliminary results of a potentially less toxic variant of the MOPPEBVCAD chemotherapy regimen for advanced Hodgkin's disease: MOPPEBVCyED, in which cyclophosphamide and etoposide replace lomustine and melphalan, respectively, with the remaining components being unaltered.

Design and Methods. The study was multicenter, prospective and randomized, and enrolled 67 patients with newly diagnosed stage IIB, III, IV Hodgkin's disease (62 were expected on the grounds of statistical considerations). Radiotherapy was restricted to sites of bulky involvement or to areas that responded incompletely to chemotherapy. Median follow-up was 48 months.

Results. Comparing MOPPEBVCAD vs. MOPPEBVCyED, the results were as follows: complete remissions 35/35 vs. 30/32 (plus one partial remission and one disease progression); relapses 5 vs. 8; deaths 2 (one of myelodysplasia) vs. 2; delivered mean dose intensity (DI): lomustine 0.79 ± 0.67 vs. cyclophosphamide 0.82 ± 0.32 ; melphalan 0.80 ± 0.13 vs. etoposide 0.86 ± 0.18 ; average DI of the 7 drugs common to both regimens 0.73 ± 0.10 vs. 0.83 ± 0.11 ; all 9 drugs 0.75 ± 0.13 vs. 0.84 ± 0.09 ($p=0.002$); projected 5-year failure-free survival 0.79 vs 0.62; second cancers, two myelodysplasias vs. one carcinoma of the kidney. Toxicities were not statistically different except for heavier thrombocytopenia being recorded with MOPPEBVCAD.

Interpretation and Conclusions. The higher cumulative and single drug DI recorded with MOPPEBVCyED may reflect better short-term tolerability, but it does not lead to better disease control. Its late toxicity may be expected to be lower in the future but at present it does not seem to be a sufficient reason to substitute MOPPEBVCyED for MOPPEBVCAD.

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Key words: Hodgkin's disease, chemotherapy

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Several multiple drug combinations which employ four to nine non-cross-resistant drugs often scheduled in alternating or hybrid regimens,¹ have been shown to induce high response rates in advanced Hodgkin's disease (80% to 90% complete remission, with 60-70% failure-free survival at 10 years). It now seems likely that further progress will be pursued with efforts aimed at increasing remission duration and improving quality of life or decreasing toxicity, rather than trying to raise the response rate further. In fact, this would require much larger study populations as the complete remission rate approaches 100%.

It is well known that the theoretical advantage of combination therapy is that different drugs given either simultaneously, or within a short time, can lead to cell death by different mechanisms, thus reducing the risk of drug resistance. This is the clinical application of the mathematical model of Goldie and Coldman regarding the drug sensitivity of tumor cells.² This model reaches its extreme exploitation in chemotherapy regimens that deliver within each cycle all the drugs originally scheduled in alternating courses, the so-called hybrid regimens, such as MOPP/ABV,³ MA/MA,⁴ ChVPP/EVA⁵ and BEACOP.^{6,7} One negative aspect of these combination therapies is the possible higher early toxicity and heavy late consequences.

Successful intensification and hybridization of Straus' alternating regimen CAD/MOPP/ABV⁸ performed by the *Italian Lymphoma Study Group* (GISL),^{9,10} combined with optional limited radiotherapy, produced interesting results. The MOPPEBVCAD schedule showed a 94% complete remission rate with tumor-specific, overall, relapse-free and failure-free survival rates at 5 years of 0.89, 0.86, 0.82 and 0.78, respectively, and remarkable but tolerable early toxicity. However, in spite of the low number of secondary tumors actually recorded so far (with a nearly 6-year median follow-up) and the low total doses scheduled for most oncogeneic drugs, the presence of three alkylating agents and a nitrosurea in the regimen has been a constant source of great concern for all investigators since the beginning of the trial.

Thus, in 1993 to explore a potentially less toxic variant of MOPPEBVCAD, possibly without reducing

its effectiveness, the GISL slightly modified the original schedule by introducing cyclophosphamide and etoposide in place of lomustine and melphalan, respectively (MOPPEBVCyED). A new randomized trial was started to compare MOPPEBVCAD with MOPPEBVCyED in advanced HD with regard to toxicity and the actual parity of response. The early 4-year results are reported here. The observed second cancers are also reported here, though the study is not yet mature for a comparison of late toxicity.

Design and Methods

Patient population

Between October 1993 and February 1996, sixty-seven patients with previously untreated, advanced HD were randomized to receive either MOPPEBVCAD (35 subjects) or MOPPEBVCyED (32 cases). Patients eligible for this study had to fulfill the following requirements: histologically proven untreated HD; age between 15 and 70 years; disease stage IIB, III or IV. Their clinical characteristics at diagnosis are listed in Table 1.

Disease stage was investigated according to the requirements of the Cotswolds Meeting.¹¹ Besides careful physical examination, patients underwent complete hematologic and biochemical screening, computed tomography of the thorax and abdomen, ultrasonography of the abdomen and unilateral bone marrow biopsy. Every clinical, radiologic or laboratory abnormality found at pretreatment staging was retested at the end of treatment to evaluate response. No patient underwent staging laparotomy with splenectomy.

Chemotherapy

The basic idea behind modifying MOPPEBVCAD to MOPPEBVCyED was that substituting two of the four drugs considered to be potentially the most myelotoxic (mechlorethamine, lomustine, procarbazine and melphalan) might be a notable step towards decreasing the risk of second tumors. Furthermore, the choice of cyclophosphamide and etoposide to replace lomustine and melphalan would also help to alleviate heavy and prolonged myelotoxicity (particularly of lomustine), which might be reflected in a higher cumulative dose intensity for the other drugs delivered. In this way, dose intensity would become the main cross-examination tool for evaluating truly reduced early hematologic toxicity. At the same time, considering the well-established effectiveness of cyclophosphamide and etoposide in HD and the anticipated increase in the cumulative dose intensity of the other drugs, improved or at least unchanged effects on clinical response could be obtained. Thus, an increase in the cumulative average dose intensity of the drugs employed in the modified regimen was chosen as the primary aim of the trial.

The doses and administration schedules for the drugs in both regimens are listed in Table 2, which also reports drug dose modifications according to blood counts. On the basis of white blood cell and platelet counts, delaying therapy was preferred to decreasing drug doses if severe myelosuppression occurred near the beginning of a new cycle, whereas

Table 1. Clinical characteristics of the study patients at diagnosis.

	MOPPEBVCAD	MOPPEBVCyED
Number	35	32
Male/female	16/19	18/14
Age		
mean±1 SD	32.7±13.5	38.4±12.9
(range)	(16 ÷ 69)	(17 ÷ 62)
Histology		
Lymphocyte predominance	1	0
Nodular sclerosis	24	20
Mixed cellularity	9	11
Lymphocyte depletion	1	1
Stage		
II B	11	7
III A	3	4
III B	9	14
IV A	6	2
IV B	6	5
Performance status	86±11	87±12
median Karnofsky index (range)		
Bulky disease	5	7
Bone marrow involvement	4	4
Hemoglobin (g/dL)	11.4±1.8	11.8±1.6
Serum LDH (U/L)	350±185	481± 330
Serum albumin (g/dL)	3.9±0.7	3.8±0.6

the opposite strategy was followed when myelosuppression appeared before completion of a cycle. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) was used strictly on clinical demand, i.e. when the neutrophil count decreased to less than $0.5 \times 10^9/L$ and fever or other signs of infection were present.

Dose intensity was calculated according to the criteria reported by Hryniuk¹² and the examples and suggestions offered by De Vita *et al.*¹³ Toxicity was measured according to standard ECOG criteria.¹⁴

Radiotherapy

On the basis of the clinical experience gained in the previous MOPPEBVCAD controlled trial, RT was not routinely associated with CT but was administered to a limited number of patients (28) and restricted to 1 or 2 selected areas corresponding to previous bulky involvement or to masses that were only slowly or partially reduced during CT. RT had to be administered after CT and the recommended total dosage could not exceed 36 Gy. In one patient a total dose of 44 Gy was reached.

Assessment of response and statistical analysis

Complete remission (CR) was defined as complete regression of measured lesions and disappearance of all other objective evidence of lymphoma for at least 3 months. Partial remission (PR) consisted of a decrease of more than 50% in the sum of the products of the diameters of measurable lesions. No response (NR) was anything less than a 50% decrease in measurable lesions.

The definition of bulky masses met the criteria coded at the Cotswolds Meeting,¹¹ i.e. for a mediastinal

Table 2. MOPPEBVCAD and MOPPEBVCyED regimens: drug doses and time scheduling, with dose reduction according to blood cell counts.

	MOPPE- BVCAD	MOPPE- BVCyED	Route	Days
	mg/m ²	mg/m ²		
Mechlorethamine (NH2)	6	6	i.v.	1 cycle 1, 3 and 5, only
Lomustine (CCNU)	100	-	p.o.	1 cycle 2, 3 and 6, only
Cyclophosphamide (CTX)	-	650	i.v.	1 cycle 2, 4 and 6, only
Vindesine (VDZ)	3	3	i.v.	1
Melphalan (Alk)	6	-	p.o.	1-3
Etoposide (VP)	-	100	p.o.	1-3
Prednisone (Pred)	40	40	p.o.	1-14
Epidoxorubicin (Epi)	40	40	i.v.	8
Vincristine (VCR)	1.4*	1.4*	i.v.	8
Procarbazine (PCZ)	100	100	p.o.	8-14
Vinblastine (VBL)	6	6	i.v.	15
Bleomycin (BLM)	10	10	i.v.	15

Leukocyte count x 10 ⁹ /L	Platelet count x 10 ⁹ /L	Drugs and doses
> 4,000	> 150	100% All drugs
3,000-3,999	100-149	100% VCR, BLM, Pred 50% VBL, VDZ, Alk, VP, NH2, Epi, CCNU, CTX, PCZ.
2,000-2,999	50-99	100% VCR, BLM, Pred 25% VDZ, VBL, Alk, VP, NH2, Epi, CTX, PCZ 0% CCNU
1,500-1,999	50-99	100% BLM, Pred 50% VCR 25% VDZ, VBL, Alk, VP, NH2, Epi, CTX, PCZ 0% CCNU
< 1,500	< 50	No drugs: re-evaluation after 1 week

*Maximum single dose limit of 2 mg. When leukocytes are less than 3.0 and/or platelets are less than 100x10⁹/L before the start of a new cycle, a 1-week delay is preferred to dose reduction.

Table 3. Means and standard deviations of the values of three multiple prognostic indexes computed for each patient at diagnosis.

Index	MOPPEBVCAD	MOPPEBVCyED	P
IPFP score	2.00 ± 1.20	2.06 ± 1.27	0.838
IDHD expected OS (months)	98.29 ± 48.44	96.28 ± 42.65	0.638
SNLG index	0.39 ± 0.19	0.40 ± 0.21	0.851

OS: overall survival.

mass, when its maximum width exceeded one third of the internal transverse diameter of the thorax at the level of the disc between vertebrae T5 and T6 and, for any extramediastinal mass, when its largest diameter was greater than 10 cm.

Using a two-sided 5% significance test (error α) with a power of the study of 90% (error β), and assuming that standard deviations of the observed dose intensity are comparable in both arms of the trial (fixed at 0.11 according to our previous experience), an expected 0.10 difference in mean dose intensity between treatments should require the enrollment of 31 patients per arm. Median follow-up was 48 months. Failure-free survival (FFS) was computed from the start of treatment to one of the following events: death from any cause, disease progression during treatment, no CR at the end of treatment, relapse after CR.¹⁵ Survival curves were calculated using the method of Kaplan and Meier.¹⁶ Standard techniques of one-way analysis of variance were used to evaluate dose-intensity differences. Data regarding toxicity grades were analyzed for possible differences with the Mann-Whitney U test,¹⁷ considering the toxicity grades from 0 to 4 as ranks of observations ordered with increasing magnitude.

Three prognostic indices specifically devised for HD were calculated for each patient to test the comparability of clinical presentation at diagnosis between the two study arms. In particular, the *International Database on Hodgkin's disease* (IDHD) estimate,¹⁸ the *Scottish and Newcastle Lymphoma Group* (SNLG) index¹⁹ and the *International Prognostic Factor Project* (IPFS) score²⁰ were computed for this reason.

Results

Sixty-seven patients were randomized to enter this study: 35 were treated with MOPPEBVCAD, 32 with MOPPEBVCyED. Patients in the two groups showed excellent prognostic comparability, as confirmed by the distribution of the main clinical characteristics (see Table 1) and by the values of the three main multiple prognostic indexes assessed before treatment (see Table 3). Response to treatment and number of recorded relapses and deaths are shown in Table 4.

Overall, 356 cycles were administered and evaluated; the mean number of cycles delivered per patient was 5.6 (range: 3 to 6) in the MOPPEBVCAD group and 5.9 (range: 4 to 6) in the MOPPEBVCyED arm. In 8 patients treatment was stopped before the sixth cycle either because of severe hematologic toxicity (5 cases, all treated with MOPPEBVCAD) or patient refusal (3 cases).

Average dose intensity for all 9 cytotoxic drugs was 0.75±0.13 (range: 0.41-1.12) in patients treated with MOPPEBVCAD and 0.84±0.09 (range: 0.69-1.00) in those given MOPPEBVCyED. This difference is statistically significant ($p = 0.002$) and, as is clear from Table 5, it is due to a generalized increase in the mean dose intensities of all the drugs rather than to selective dose elevation of cyclophosphamide and etoposide, which replaced lomustine and melphalan in the modified regimen. Only vincristine doses did not differ in the two regimens, probably due to the fact that the 2 mg maximal dose limit that was

Table 4. Treatment results after a nearly 4-year median follow-up.

	MOPPEBVCAD	MOPPEBVCyED
Patients treated	35	32
Complete response	35	30
Partial response	0	1
Null response	0	1
Progression	0	0
Relapse	5	8
Death	2	2
Second neoplasia	2	1

Table 5. Mean delivered dose intensities (±SD) of each drug in the two regimens.

Drugs	MOPPEBVCAD	Drugs	MOPPEBVCyED	p
Lomustine	0.79±0.67	Cyclophosphamide	0.82±0.32	-
Melphalan	0.80±0.13	Etoposide	0.86±0.18	-
Mechlorethamine	0.68±0.22		0.85±0.22	0.005
Vindesine	0.76±0.19		0.87±0.11	0.010
Epidoxorubicin	0.82±0.16		0.90±0.12	0.023
Vincristine	0.70±0.16		0.73±0.18	0.404
Procarbazine	0.77±0.18		0.86±0.12	0.044
Vinblastine	0.59±0.13		0.70±0.17	0.006
Bleomycin	0.82±0.16		0.90±0.12	0.042
All 9 drugs	0.75±0.13		0.84±0.09	0.002
7 drugs common to both regimens	0.73±0.10		0.83±0.11	0.010

observed is far from the toxicity threshold for many patients. Figure 1 shows the mean length of the intervals between cycles. The time differences between regimens were not statistically significant; however, the longer mean delivery time for the entire MOPPEBVCAD regimen – and consequently its lower average dose intensity – appear to be mainly due to the greater length of the second and fourth cycles, which is probably related to the prolonged hematologic toxicity of lomustine.

Table 6 shows the toxicity associated with the two regimens. Toxic manifestations were generally well tolerated and reversible; hematologic toxicity was relatively more severe and more frequently dose-limiting. Thirty-one patients in all (20 treated with MOPPEBVCAD, 11 with MOPPEBVCyED) received at least a few days of therapy with G-CSF or GM-CSF. Thrombocytopenia was the only side effect which demonstrated a statistically significant higher incidence among patients treated with MOPPEBVCAD ($p=0.02$). Non-hematologic toxicity was mild and tolerable, and very rarely reached grade 3-4 severity for any of the parameters considered. Nausea and/or vomiting were well controlled with the use of anti-serotonergic-receptor drugs. Neurotoxicity required dose reduction of vincristine and vinblastine in 12 subjects (7 in the MOPPEBVCAD group, 5 in the MOPPEBVCyED arm). Mucositis was always mild and no patient showed anthracycline-related cardiotoxicity.

RT was administered to 28 patients (41%): 13 treated with MOPPEBVCAD and 15 with MOPPEBVCyED, and 27 out of these 28 were judged to be in CR after completion of chemotherapy, before RT.

Figure 2 shows the FFS recorded in both treatment groups; no clear-cut, statistically significant differ-

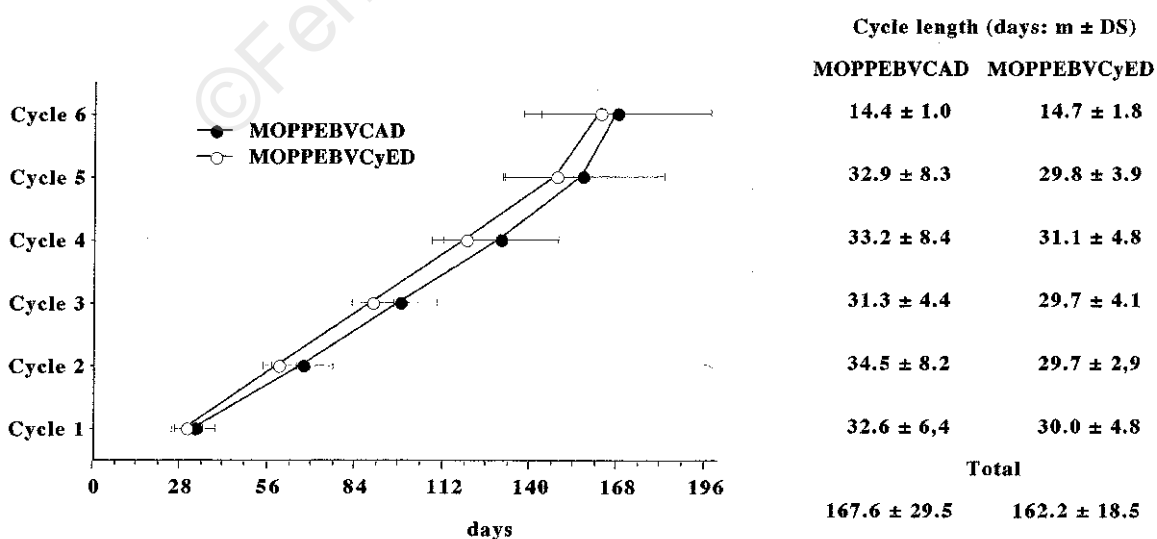


Figure 1. Cumulative and individual length of the 6 cycles of the two chemotherapy regimens.

Table 6. Main hematologic and non-hematologic toxicity recorded during administration of the two chemotherapy regimens (Mann-Whitney U test).

Toxicity		ECOG grades					p
		0	1	2	3	4	
Anemia	MOPPEBVCAD	21	4	4	6	1	0.7033
	MOPPEBVCyED	14	9	7	2	0	
Leukopenia	MOPPEBVCAD	9	2	5	12	8	0.5189
	MOPPEBVCyED	5	4	10	9	4	
Thrombocytopenia	MOPPEBVCAD	23	2	2	5	4	0.0227
	MOPPEBVCyED	31	0	0	0	1	
Nausea/vomiting	MOPPEBVCAD	20	6	9	0	1	0.9510
	MOPPEBVCyED	15	13	4	0	0	
Neurological	MOPPEBVCAD	21	8	6	0	1	0.6406
	MOPPEBVCyED	20	8	4	0	0	
Cardiac	MOPPEBVCAD	36	0	0	0	0	> 0.9999
	MOPPEBVCyED	32	0	0	0	0	
Pulmonary	MOPPEBVCAD	34	0	2	0	0	0.6942
	MOPPEBVCyED	32	0	0	0	0	

ences emerged even though a trend toward poorer control of the disease was recorded for the MOPPEBVCyED group. Among the 65 patients achieving CR, relapses were recorded in 13: 5 in the group treated with MOPPEBVCAD (at 3, 4, 4, 30, and 34 months after the end of therapy) and 8 in the group treated with MOPPEBVCyED (after 4, 12, 20, 21, 23, 27, 33, and 37 months). Two patients treated with the modified regimen died: one of disease progression, the other of relapse 10 months after the end of therapy. Two patients treated with MOPPEBVCAD also died: one of myelodysplastic syndrome and one of relapse 46 months after the end of therapy. Three second cancers were recorded: two myelodysplastic syndromes (both in the MOPPEBVCAD arm) and one clear cell carcinoma of the kidney (in the MOPPEBVCyED group).

Discussion

The present trial tested a modified version of the MOPPEBVCAD chemotherapy regimen for advanced HD designed to deliver fewer myelotoxic drugs with two aims: to increase the cumulative dose intensities actually received of all the drugs by limiting myelotoxicity and, if possible, to reduce the expected incidence of second neoplasias. Now, after a 4-year median follow-up, the data are mature for evaluation of early toxicity and response.

As a matter of fact, cyclophosphamide and etoposide, which in MOPPEBVCyED replace lomustine and melphalan, did clearly lower hematologic toxicity, thus making it possible to deliver significantly higher mean cumulative dose intensities of all the other drugs common to both regimens. Furthermore, even the given/projected dose intensity rates of cyclophosphamide and etoposide in the modified regimen were a little higher than those of lomustine and melphalan

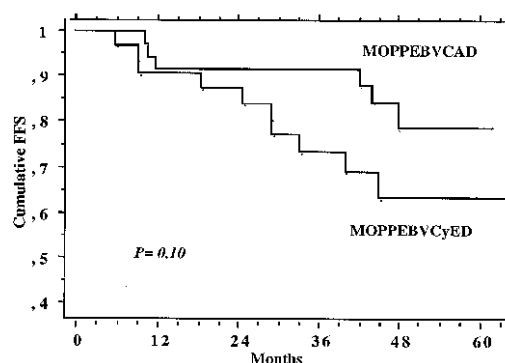


Figure 2. Cumulative failure-free survival (FFS) of the two groups of patients compared.

in the original. Therefore none of the drugs in the MOPPEBVCyED regimen was actually administered without true dose intensification, which ranged from +0.03 (for cyclophosphamide and vincristine) to +0.17 for mechlorethamine. However, nothing in the recorded response rates and 4-year FFS has reflected positively the approximately 12% average increase in cumulative dose intensity delivered, which can be considered a truly remarkable gain when related to the number of drugs involved and to the multicenter outpatient nature of the investigation. Moreover, even though the differences in outcome parameters recorded were not statistically significant, a trend toward somewhat lower effectiveness for the modified regimen as compared to the original can be identified.

No prognostic differences emerged between the two groups of patients, thus excluding the possibility that unbalanced pretreatment parameters played a role in clinical results. The use of RT was nearly identical in the two series with respect to number of patients irradiated, field extension and doses delivered. So the differences in results can be reasonably ascribed to differences in the chemotherapy regimens.

The present data should not be considered to conflict with the concept of dose intensity; they only give some evidence that a constant and direct relationship between dose intensity and clinical response may be hard to demonstrate. Alternatively, if we accept the basic assumption of the dose intensity computation according to which relative dose intensities of different drugs within a regimen can be arithmetically managed, then we must point out that an average 12% increase in dose intensity of the 7 drugs common to both regimens is not able – in spite of the addition of adequate doses of cyclophosphamide and etoposide – to balance the removal of lomustine and melphalan. It is noteworthy that the individual projected doses of these two drugs were comparable with, or even higher than, those currently administered in several other regimens active in HD. For example, lomustine (given at a dose of 100 mg/m² in the MOPPEBVCAD scheme) is administered at 75 mg/m² in the CVPP regimen,^{21,22} which proved to be superior to MOPP,²³ MVPP and COPP with respect to response rate, toxi-

city and remission duration.²² Similarly, a single dose of lomustine has been established at 60 mg/m² in the PACET regimen,²⁴ 80 mg/m² in CEP chemotherapy,²⁵ and 100 mg/m² in the SCAB,²⁶ CEM²⁵ and LVB²⁷ schedules. Melphalan has been used less frequently in HD, but it was administered for 4 days per cycle at 7.5 mg/m² in the PAVE²⁸ regimen and at 6 mg/m² in the CAD schedule.⁷ Cyclophosphamide was generally given at a dose of 650 mg/m² when it substituted mechlorethamine,²⁹ whereas etoposide was given orally at a 3-day dose of 100 mg/m²/day in the CEM²⁵ and CEP²⁵ regimens, intravenously at the same dosage in the MIME³⁰ and VEEP³¹ schedules or at 105 mg/m² in ABEP³² chemotherapy.

While no information is available in the literature regarding the possibility that cyclophosphamide and/or etoposide show lower activity in HD than lomustine and/or melphalan, great concern is documented about the oncogenic risk linked to the use of these last two drugs. This risk is further reflected by the present work, which reports two second tumors (myelodysplastic syndromes) in the MOPPEBVCAD arm of the trial vs. one (renal) in the MOPPEBVCyED group, in spite of the fairly brief (4 years) mean follow-up. Of course the difference in second tumor incidence is insignificant.

Now, at 7 years from the start of the trial, it is clear that the study has substantially failed in its main object – to reduce the toxicity of MOPPEBVCAD without reducing its effectiveness. Perhaps we succeeded in correctly identifying the most toxic drugs in the regimen and, after proper substitutions, were able to reduce early toxicity, increase general dose intensity and hopefully limit the risk of second tumor, but we have been paying for these achievements with a notable decline in effectiveness – though it is not yet statistically significant. We actually need better knowledge about the specific effectiveness of each antitumoral drug in relation to doses and delivery intervals. For the purposes of designing a clinical trial, basic single-agent dose-response information would be very useful. It should be specific for individual tumors as was the one proposed by Hryniuk *et al.*³³ for metastatic breast cancer. It should also be integrated with a single-drug dose-related oncogenic power scale (or score) for adult HD patients, similar to the one devised by Meadows *et al.*³⁴ in children. The choice of the drugs to be used and their dose and scheduling should ideally take all this information into account in order to maximize results while minimizing late consequences.

At present, we cannot state that MOPPEBVCyED is equally active in advanced HD as MOPPEBVCAD, but only that it is less toxic and, probably, a little less active. Conversely, our data confirm the extreme effectiveness of MOPPEBVCAD, which in separate studies has shown clinical outcome figures among the highest recorded in multicenter trials for advanced HD. Our results with MOPPEBVCAD (present study: CR 100%, 5-year FFS: 0.79; previous GISL trial:^{2,3} CR 94%, 6-year FFS: 0.78) have been paralleled only by GHSG data with escalated BEACOPP^{8,9} (CR 93%, 23-months FFS: 0.84). The number of second tumors hitherto recorded in trials with MOPPEBVCAD is comparable to that of alternated

MOPP/ABVD²⁹ or ChIVPP,³⁵ probably due to the fact that, as already pointed out, the number of potentially oncogenic drugs employed is counterbalanced by their low cumulative absolute doses as well as by the less frequent association of RT delivered to limited fields and in limited doses. However, a more prolonged follow-up is crucial for settling this point.

Contributions and Acknowledgments

PGG designed the study. All the authors were responsible for patients' clinical management. PGG, CB and MLG performed the statistical analyses. PGG and CB wrote the paper. RB, EI and LC revised the manuscript; RB, MPP, SM, FA, EI, NDR, LC helped to interpret the data and to discuss the results. EA revised the paper and gave final approval for its submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- The study indirectly suggests how the tolerability of the MOPPEBVCAD regimen might be improved without reducing effectiveness. Further, it shows that a direct relationship between dose intensity of a drug and clinical response may be undemonstrable or, alternatively, that the dose intensities of several drugs must be differently considered in relation to clinical response.

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