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ORIGINAL REPORT

ABVD Versus Modified Stanford V Versus MOPPEBVCAD With Optional and Limited Radiotherapy in Intermediate- and Advanced-Stage Hodgkin's Lymphoma: Final Results of a Multicenter Randomized Trial by the Intergruppo Italiano Linfomi

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ABSTRACT

Purpose

In this multicenter, prospective, randomized clinical trial on advanced Hodgkin's lymphoma (HL), the efficacy and toxicity of two chemotherapy regimens, doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (Stanford V) and mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (MOPPEBVCAD), were compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as standard therapy to select which regimen would best support a reduced radiotherapy program, which was limited to ≤ two sites of either previous bulky or partially remitting disease (a modification of the original Stanford program).

Patients and Methods

Three hundred fifty-five patients with stage IIB, III, or IV HL were randomly assigned. Three hundred thirty-four patients were assessable for the study and received six cycles of ABVD (n = 122), three cycles of Stanford V (n = 107), or six cycles of MOPPEBVCAD (n = 106); radiotherapy was administered to 76, 71, and 50 patients in these three arms, respectively.

Results

The complete response rates for ABVD, Stanford V, and MOPPEBVCAD were 89%, 76% and 94%, respectively; 5-year failure-free survival (FFS) and progression-free survival rates were 78%, 54%, 81% and 85%, 73%, and 94%, respectively ($P < .01$ for comparison of Stanford V with the other two regimens). Corresponding 5-year overall survival rates were 90%, 82%, and 89% for ABVD, Stanford V, and MOPPEBVCAD, respectively. Stanford V was more myelotoxic than ABVD but less myelotoxic than MOPPEBVCAD, which had larger reductions in the prescribed drug doses.

Conclusion

When associated with conditioned and limited (not adjuvant) radiotherapy, ABVD and MOPPEBVCAD were superior to Stanford V chemotherapy in terms of response rate and FFS and progression-free survival. Patients were irradiated less often after MOPPEBVCAD, but this regimen was more toxic. ABVD is still the best choice when it is combined with optional, limited irradiation.

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INTRODUCTION

The treatment of patients with advanced-stage Hodgkin's lymphoma (HL) is still a challenge for clinicians. The major therapeutic difficulty is raised by the proportion of patients (approximately 20% to 30%) who are resistant to first-line treatment or

relapse after remissions of variable duration. Several trials have been conducted to identify the therapy with the best risk-to-benefit ratio, thus increasing the efficacy of treatment while minimizing the risk of late toxicity. Many of the tested chemotherapy combinations, which were derived from the standard regimen of the 1970s and 1980s (mechlorethamine, vincristine, procarbazine, and prednisone [MOPP]) and/or from the standard regimen used in the 1990s (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]), were compared with variably modified schedules derived from these well-tested models or regimens originally devised for advanced-stage disease. Fundamentally, the results of these studies were that alternating MOPP/ABVD and ABVD are equally effective and both are superior to MOPP alone[1,2] and that MOPP/doxorubicin, bleomycin, and vinblastine (ABV) is more effective than sequential MOPP/ABVD[3] but as effective as alternating MOPP/ABVD[4] and ABVD alone,[5] which, however, showed lower toxicity. Failure-free survival (FFS) rates at 5 years varied from 60% to 70% for the three treatments, and in a more recent study,[6] event-free survival was reached by 75% of an unselected cohort of stage III and IV patients treated with MOPP/ABV plus involved-field radiotherapy. Furthermore, the combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)[7] produced a significantly higher 5-year FFS rate (76% with the basic schedule and 87% with the intensified schedule) than alternating COPP/ABVD (69%), which is a variant of the MOPP/ABVD regimen in which cyclophosphamide replaces mechlorethamine. However, there is still some concern about the possible late toxicity of BEACOPP because the latest available update has only reached a median follow-up of 60 months. Overall, these results indicate that ABVD should still be considered the standard regimen for the treatment of advanced-stage HL.[8] Other new schedules of multiple drugs have also demonstrated marked effectiveness in advanced disease, with 5-year FFS rates ranging from 72% to 89%. The doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (Stanford V)[9]; MOPP plus epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (MOPPEBVCAD)[10,11]; etoposide, vinblastine, and doxorubicin[12]; etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone[13]; and chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine and etoposide[14] regimens were each designed with somewhat different rationales and are worth comparing with ABVD. The Stanford V regimen, by virtue of continuous exposure to active drugs on a weekly basis, actually shortens the duration of chemotherapy to only 3 months.[9] In 1987, the MOPPEBVCAD regimen was an early attempt to intensify and hybridize some well-known and active available chemotherapy regimens to increase their efficacy.[11] Both the Stanford V and the MOPPEBVCAD regimens produced particularly interesting results.

Here, we report the results of a prospective, randomized, multicenter trial on the treatment of advanced-stage HL comparing the ABVD, Stanford V, and MOPPEBVCAD chemotherapy regimens in combination with a limited radiotherapy program delivered according to criteria of disease bulk and/or response. Because these criteria were more restrictive than those devised in the original Stanford V combination therapy, this program must be considered as a modification of the radiotherapy part of the Stanford V protocol.

PATIENTS AND METHODS

Eligibility

Previously untreated patients aged 16 to 65 years with a biopsy-proven diagnosis of HL and clinical stage IIB, III, or IV disease were eligible for random assignment. Normal cardiac, pulmonary, hepatic, and renal function was also required unless any abnormal function was considered to be directly related to the HL. Pregnant or lactating women and patients with a history of malignancy, a positive HIV test, or an Eastern Cooperative Oncology Group performance status greater than 3 were ineligible. Patients with anaplastic, $CD30^+$, large-cell lymphoma were also excluded from study.

Staging

All patients were clinically staged according to the Cotswolds modifications of the Ann Arbor criteria.[15] Clinical staging procedures included a full history and physical examination, plain radiography of the chest, ultrasonography of the abdomen, computed tomography scans of the thorax, abdomen, and pelvis, full blood count and biochemical profile of the serum, examination of a bone marrow aspirate, and trephine biopsy. Isotopic and ultrasound scans and biopsies of suspicious lesions were performed when necessary. Splenic involvement was assessed only in the presence of focal defects (single or multiple) that ultrasonography and computed tomography with nonionic contrast medium had shown to be neither cystic nor vascular. Bulky disease was defined as a mass with a diameter of 6 cm or more according to a definition rather more restrictive for therapeutic purposes than that given at the Cotswolds Meeting.[15]

Patients, Randomization, and Treatment

Between January 1996 and April 2000, 355 patients were registered and gave written informed consent for their participation in the study. These patients were enrolled by four cooperative Italian groups (Gruppo Italiano Studio Linfomi, Gruppo Multiregionale Studio Linfomi, Non-Hodgkin's Lymphoma Cooperative Study Group, and Gruppo Lombardo Studio Linfomi). The annual enrollment rate was 23% in 1996, 23% in 1997, 27% in 1998, 25% in 1999%, and 3% in the first 4 months of 2000. Patients were randomly assigned to receive six courses of ABVD (126 patients), 12 weeks of therapy according to the Stanford V schedule (115 patients), or six cycles of MOPPEBVCAD (114 patients). Simple random assignment was adopted, and each cooperative group's secretariat managed the prepared lists of random sequences. Communication regarding eligibility and allocation was made by telephone. The fact that each group enrolled and randomly assigned different numbers of patients along the list sequences explains the slight differences in the number of allocated patients per arm. One patient, who was randomly assigned to

MOPPEBVCAD treatment, was discovered to have non-HL after pathologic review; his treatment was changed accordingly after the second cycle, and this patient was excluded from the study. Eight patients (five receiving the modified Stanford V program and three receiving the MOPPEBVCAD combination therapy) withdrew consent early or emigrated to another country, and 11 patients were not assessable because no data other than those of registration were available (four in the ABVD arm, three in the Stanford V arm, and four in the MOPPEBVCAD arm). Thus, 335 assessable patients (ABVD, n = 122; Stanford V, n = 107; and MOPPEBVCAD, n = 106) form the basis of this report as far as clinical response and toxicity are concerned, whereas 354 patients (ie, all patients but the patient with inconsistent histology) were analyzed according to intent to treat.

Drug doses and administration schedules are listed in Table 1. The main staging and prognostic characteristics of the assessable patients, divided by treatment arm, are listed in Table 2. The MOPPEBVCAD arm contained a lower percentage of patients with stage IIB disease, mediastinal bulk, and nodular sclerosis histologic type than the other two arms, but it included a higher proportion of stage III patients.

Allopurinol (300 mg/d) and an abundant fluid intake were prescribed. Prophylactic antibiotics were not administered in the ABVD and MOPPEBVCAD arms, whereas ciprofloxacin (500 mg twice a day), fluconazole (100 mg once a day), and trimethoprim (80 mg) with sulfamethoxazole (400 mg) three times a week were suggested beginning from the fourth week of therapy with the Stanford V regimen, according to the original experience of Bartlett et al.[16]

Table 1. Drug Doses and Time Schedules of the Three Chemotherapy Regimens Investigated in the Study

Drug	Dose (mg/m^2)	Route	Days
ABVD*			
Doxorubicin	25	IV	1, 15
Bleomycin	5	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Stanford V			
Doxorubicin	25	IV	1, 15
Vinblastine†	6	IV	1, 15
Mechlorethamine	6	IV	1
Etoposide	60	IV	15, 16
Vincristine‡	1.4	IV	8, 22
Bleomycin	5	IV	8, 22
Prednisone§	40	PO	Every other day
MOPPEBVCAD*			
Mechlorethamine	6	IV	1, cycles 1, 3, and 5 only
Lomustine	100	PO	1, cycles 2, 4, and 6 only
Vindesine	3	IV	1
Melphalan	6	PO	1-3
Prednisone	40	PO	1-14
Epidoxorubicin	40	IV	8
Vincristine	1.4	IV	8
Procarbazine	100	PO	8-14
Vinblastine	6	IV	15
Bleomycin	10	IV	15

Abbreviations: IV, intravenous; PO, orally.
*Cycles were repeated every 28 days; day 29 was the start of a new cycle. The planned number of cycles was six for ABVD and MOPPEBVCAD and three for Stanford V.
†Vinblastine dose decreased to 4 mg/m^2 during cycle 3 for patients greater than 50 years of age.
‡Vincristine dose decreased to 1 mg/m^2 during cycle 3 for patients greater than 50 years of age.
§Prednisone dose tapered by 10 mg every other day starting at day 16 in the third cycle.

Growth factors were not permitted routinely but used only in patients with severe neutropenia ($< 0.5 \times 10^9$/L) associated with fever or other signs of infection. When growth factors were necessary, they were administered at the lowest effective doses only in the following restricted time intervals: from days 3 to 11 and 17 to 25 in the ABVD regimen, from days 16 to 25 in the MOPPEBVCAD regimen, and from days 4 to 13 and 17 to 26 in the Stanford V 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.

A first evaluation of response was planned after four cycles of ABVD or MOPPEBVCAD and after two cycles of the Stanford V schedule (ie, approximately 16 and 8 weeks, respectively, from the start of treatment). Only patients who were found to have responded completely or partially at this intermediate evaluation continued the treatment; otherwise, they were admitted to salvage therapies. A full restaging evaluation was performed at the end of chemotherapy, and all investigations with initially abnormal results were repeated. Response was determined according to the conventional criteria for complete remission (CR), uncertain complete remission (CRu), partial remission (PR), no response, and progressive disease codified at the Cotswolds Meeting.

To test which chemotherapy schedule would better tolerate the projected reduction of the subsequent radiotherapy, we had to condition the administration of the radiation to some basic information regarding both initial staging and response to chemotherapy. Thus, patients who responded to chemotherapy were administered radiotherapy to sites of previous bulky disease or to sites that responded partially to chemotherapy. The only condition for starting the radiotherapy program was that there were no more than two sites to treat. Only in the case of an unequivocal CR to chemotherapy were clinicians authorized to renounce the radiotherapy. This means that patients classified as having CRu because of slight radiologic enlargements in no more than two sites were irradiated. Radiotherapy had to start 4 to 6 weeks after the end of chemotherapy. The recommended total doses were 36 Gy to areas with no sure signs of disease at the end of chemotherapy (patients in CR or CRu) and 42 Gy to sites with partially persisting disease.

Within 6 weeks after finishing the radiotherapy, restaging was completed with clinical and instrumental re-evaluation of the irradiated sites to assess the final response. On completion of all treatments, patients were reviewed on a regular basis (every 3 months in the first year and every 6 months in the following years, unless signs or symptoms of possible recurrence required a more intensive follow-up).

Statistics

Stanford V and MOPPEBVCAD were considered the experimental regimens and were tested against ABVD primarily in terms of FFS. The failure rate expected from ABVD was estimated to be 35% at 5 years, and a reduction to 15% by at least one of the other two regimens was considered clinically valuable and worth testing. Using a one-sided 5% significance test (error α) and a power of the study of 80% (error β), 90 patients were required in each arm (270 patients in all) to test the hypothesis.

Table 2. Clinical Characteristics of the 333 Patients by Treatment Arm

Characteristic	ABVD (n = 122)		Stanford V (n = 107)		MOPPEBVCAD (n = 106)		Total No. of Patients (N = 335)
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Sex							
Male	70		66		55		191
Female	52		41		51		144
Age, years							
Median	31		34		34		34
Range	16-68		17-69		15-65		15-69
> 45 years	28	23	27	25	36	34	92
Histology							
LP	0	0	5	5	7	7	12
NS	95	78	76	71	66	62	236
MC	18	15	20	19	27	25	65
LD	3	2	4	4	2	2	9
Unclassifiable	6	5	2	1	5	5	13
Stage							
IIB	41	34	45	42	26	25	112
IIIA	26	21	25	23	23	22	74
IIIB	27	22	11	10	32	30	70
IVA	8	7	6	6	11	10	25
IVB	20	17	20	19	14	13	54
Bulk							
Mediastinal	32	26	28	26	19	18	79
Extramediastinal	6	5	4	4	3	3	13
Splenic involvement	25	20	22	21	22	21	69
Bone marrow involvement	11	9	9	8	12	11	32
Other extranodal involvement	45	37	47	44	41	39	133
Hemoglobin < 10.5 g/dL	24	20	16	15	22	21	62
LDH > normal limits	32	26	31	29	34	32	129
IPS							
0-1	46	38	37	35	37	35	120
2-3	59	48	60	56	58	55	177
≥ 4	17	14	10	9	11	10	38

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone; MOPPEBVCAD, mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin; LP, lymphocytic predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocytic depletion; LDH, lactate dehydrogenase; IPS, International Prognostic Score.

Toxicity was measured according to the standard Eastern Cooperative Oncology Group criteria.[17] Overall survival (OS) was computed from the date of diagnosis to the date of last observation or death (from any cause). Relapse-free survival (RFS) for complete responders was measured from the date of therapy completion to the date of last observation or relapse. FFS was determined from the start of treatment to last follow-up or to one of the following events: death from any cause, disease progression during treatment, any response other than CR at the end of therapy, or relapse. Freedom from progression (FFP) was calculated from the start of treatment to disease progression or relapse or to the last follow-up.

Survival curves were calculated using the Kaplan-Meier method,[18] and statistical comparisons between curves were made using the log-rank test (the level of statistical significance was set at a two-sided $P < .05$). Deaths as a result of causes other than HL or therapy were not censored from the OS and FFS analyses.[19]

The dose-intensity of each drug and each regimen was calculated according to the criteria reported by Hryniuk[20] and the examples and suggestion furnished by DeVita et al.[21] The International Prognostic Score[22] was calculated for all assessable patients. χ^2 analysis, when appropriate, and Fisher's exact test[23] were used to evaluate differences between normally distributed variables, whereas the Kruskal-Wallis[23] test was applied to continuous data without a normal distribution.

RESULTS

Response to Therapies, Acute Toxicity, and Dose-Intensity

Table 3 lists both the responses to chemotherapy and the final responses to the postchemotherapy radiotherapy, when administered. The clinical evaluation after chemotherapy alone showed rather varied results. MOPPEBVCAD and ABVD were associated with higher CR rates (81% and 71%, respectively) than the Stanford V chemotherapy (56%),

Table 3. Response Recorded at the End of CT and at the End of the Post-CT RT (if any)

Response	ABVD			Stanford V			MOPPEBVCAD		
	CT	+RT		CT	+RT		CT	+RT	
	(No.)	No.	%	(No.)	No.	%	(No.)	No.	%
Total No. of patients	122	76/122		107	71/107		106	50/106	
CR*	70	109	89	38	81	76	56	100	94
CRu*	17			22			26		
PR*	27	4	3	35	8	7	21	3	3
NR	5	6	5	7	9	8	0	0	
PD	3	3	3	1	5	5	0	0	
NA				4†		4	3‡		3

Abbreviations: CT, chemotherapy; RT, radiotherapy; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone; MOPPEBVCAD, mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin; CR, complete remission; CRu, uncertain complete remission; PR, partial remission; NR, no response; PD, progressive disease; NA, response not assessable.

*The number of patients in CR, CRu, or PR after chemotherapy who were irradiated because of their bulky presentation were 29 (ABVD), 17 (Stanford V), and 21 (MOPPEBVCAD); the number of patients not irradiated because of responses less than PR after chemotherapy were eight (ABVD), eight (Stanford V), and zero (MOPPEBVCAD); the number of patients not irradiated because of PR in more than two involved sites were four (ABVD), 14 (Stanford V), and 16 (MOPPEBVCAD).

†Chemotherapy interruption as a result of toxicity.

‡Toxic deaths.

whereas, even when computing severe toxic events as therapy failures, MOPPEBVCAD had the lowest failure rate (3%), with the failure rates of ABVD and Stanford V being higher (8% and 16%, respectively). After radiotherapy, CR rates were 94%, 89%, and 76% for the MOPPEBVCAD, ABVD, and Stanford V arms, respectively. Hematologic toxicity (Table 4) was mild for ABVD, moderate for Stanford V, and substantial for MOPPEBVCAD. The differences are statistically significant ($P < .01$). Nonhematologic toxicity was similarly moderate in all three arms (Table 4). In particular, patients on the MOPPEBVCAD regimen did not seem to pay a significant price in neurotoxicity for the three different vinca alkaloids incorporated into the schedule. The Stanford V chemotherapy had to be discontinued in four patients because of severe toxicity; two patients developed hepatic toxicity, one developed tuberculosis of the bones with involvement of a thoracic vertebra, and one had recurrent pulmonary infections. All these four patients were rescued with other conventional chemotherapy regimens. In the MOPPEBVCAD arm, there were three deaths during treatment; one 35-year-old male died of generalized sepsis, one 61-year-old male died suddenly, probably of a cardiac event, and one 51-year-old female died of the consequence of a major protocol violation (on day 1 of the first cycle, she was administered lomustine, which should have been administered in the second cycle, together with all the drugs scheduled for the same day of the first cycle, which were mechlorethamine, vindesine, melphalan, and prednisone; the patient developed severe bone marrow hypoplasia, which prevented any further chemotherapy administration, and she actually died of sepsis 2 months later with presence of disease).

Table 4. Grade 3 and 4 Acute Hematologic and Nonhematologic Toxicity by Chemotherapy Arm

Toxicity	ABVD		Stanford V		MOPPEBVCAD	
	No.	%	No.	%	No.	%
Hematologic						
Anemia	0	0	16	15	20	19
Leukopenia	13	11	31	29	54	51
Neutropenia	30	25	31	29	54	51
Thrombocytopenia	0	0	1	1	25	24
Infections	1	1	0	0	15	14
Nonhematologic						
Neurologic, sensory	3	2	8	7	9	9
Constipation	0	0	4	4	2	2
Nausea/vomiting	6	5	4	4	7	7
Alopecia	0	0	1	1	1	1

NOTE. Percentages calculated from the total number of patients in each arm.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone; MOPPEBVCAD, mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin.

The average relative dose-intensities of the three regimens varied slightly (ABVD = 0.83, Stanford V = 0.81, and MOPPEBVCAD = 0.73), but considering the different number of drugs administered, the frequencies of administration, and the mechanisms of action of the drugs involved, these differences were expected from the preceding experiences and, nevertheless, demonstrate the substantially comparable compliance of both clinicians and patients towards the three different treatments.

Radiotherapy to sites of previous bulky disease or incomplete response to chemotherapy was administered to 197 of all the assessable patients (59%) and to 76 patients (62%) after ABVD, 71 patients (66%) after Stanford V, and

50 patients (47%) after MOPPEBVCAD. The median interval between the end of chemotherapy and the start of irradiation was 6 weeks, irrespective of the regimen administered. One hundred forty patients had their response status changed from CRu or PR to CR after radiotherapy (49 patients in the ABVD arm, 47 in the modified Stanford V arm, and 44 in the MOPPEBVCAD arm), whereas irradiation was not able to improve PR or to avoid progression of disease in five patients treated with ABVD, in 10 patients treated with Stanford V, and in three patients treated with MOPPEBVCAD. No severe adverse effects of irradiation were recorded during and/or early after these short courses of irradiation.

Disease Control, Late Toxicity, and Follow-Up Data

The median follow-up time of the whole population of alive patients was 61 months (range, 7 to 95 months). Table 5 lists the failures recorded by treatment arm. The modified Stanford V arm showed the highest rate of early failures (24%), whereas MOPPEBVCAD therapy had the lowest rate (3%), although the unavoidably unbalanced early assessment of response must be considered. Patients treated with the modified Stanford V combination regimen showed the highest percentage of relapses (21%), whereas patients treated with MOPPEBVCAD had the lowest relapse rate (7%) and the highest rate of deaths in CR (7%). However, the only three early deaths were recorded in this arm. No cases of late cardiac or pulmonary toxicity have so far occurred.

Of the 12 patients who died in CR, one was in the ABVD arm, three were in the modified Stanford V arm, and eight were in the MOPPEBVCAD arm. Six deaths were a result of causes not directly related to the disease or to early consequences of treatment; one patient in the ABVD arm died of liver cirrhosis 53 months after the end of therapy, four patients treated with MOPPEBVCAD died (one patient each died of generalized sepsis, interstitial pneumonia, progressive multifocal leukoencephalopathy, and stroke after follow-up periods of 25, 15, 17, and 21 months, respectively), and one patient in the modified Stanford V arm who had chronic obstructive pulmonary disease died of acute respiratory failure 55 months after the treatment for HL.

Six patients with fatal metachronous tumors have been recorded so far. Four patients treated with MOPPEBVCAD developed acute myeloid leukemia and died of it 22, 39, 41, and 67 months after the cessation of therapy (karyotypes are not available). Two patients died 23 and 32 months after the end of Stanford V plus radiotherapy; one of these patients died of a large-cell non-HL, and the other patient died of pancreatic adenocarcinoma. No other second tumors have so far been identified in living patients.

The OS of the 354 eligible patients, divided by trial arm, is illustrated in Figure 1. The projected 5-year survival was similar in the three arms, ranging from 82% (Stanford V) to 90% (ABVD). The analysis of the FFP (Fig 2) shows that the modified Stanford V program controls disease (FFP, 73% at 5 years) less effectively than ABVD (85%) and much less effectively than MOPPEBVCAD (94%). These differences are wider among the FFS curves, which are shown in Figure 3. In this analysis, the account of deaths from any cause and responses other than CR as events increases the differences among the ABVD and MOPPEBVCAD arms (5-year FFS, 78% and 81%, respectively) and the modified Stanford V arm (54%). As illustrated in Figure 4, the MOPPEBVCAD and ABVD regimens were found to maintain achieved CRs better than the Stanford V schedule (5-year RFS, 92%, 88%, and 73%, respectively). The observed differences in terms of FFS and FFP among the three treatments are substantially the same within groups of patients with either a low (0 to 2) or high ($\geq$ 3) International Prognostic Score.

DISCUSSION

Since 1995, the true impact on survival of adding radiotherapy to the available chemotherapy for advanced-stage HL has begun to be questioned,[24] and the risk of second solid tumors, mainly related to radiotherapy and showing a constant increase over 20 years from the end of therapy, has become clear.[25,26] Above all, it is still not clear whether the benefit of postchemotherapy irradiation is actually demonstrable in all patients[27] or in partial responders only.[6] The

Table 5. List of the Failures Recorded in the Three Treatment Arms of the Study

Treatment Failure	ABVD		Stanford V		MOPPEBVCAD	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Early treatment failure	13	11	26	24	3	3
Early death	0	0	0	0	3	3
Relapse	12	10	23	21	7	7
Death in complete remission	1	1	3	3	8	8

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone; MOPPEBVCAD, mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin.

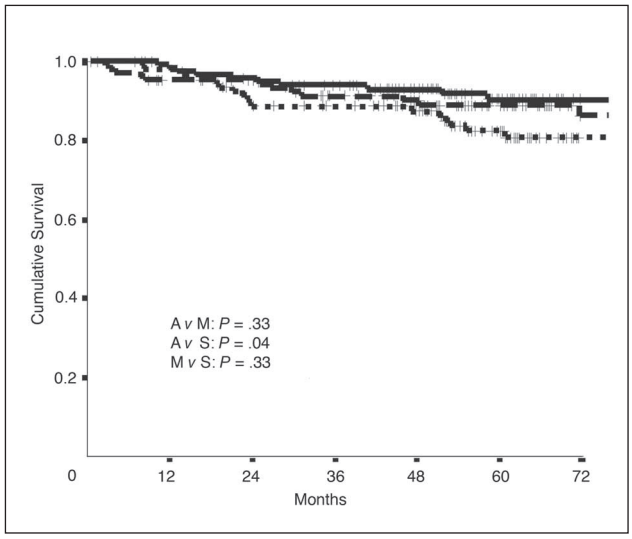

Fig 1. Overall survival by treatment arm. Continuous line: doxorubicin, bleomycin, vinblastine, and dacarbazine (A; 126 patients); dashed line: mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (M; 113 patients); dotted line: doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (S; 115 patients).

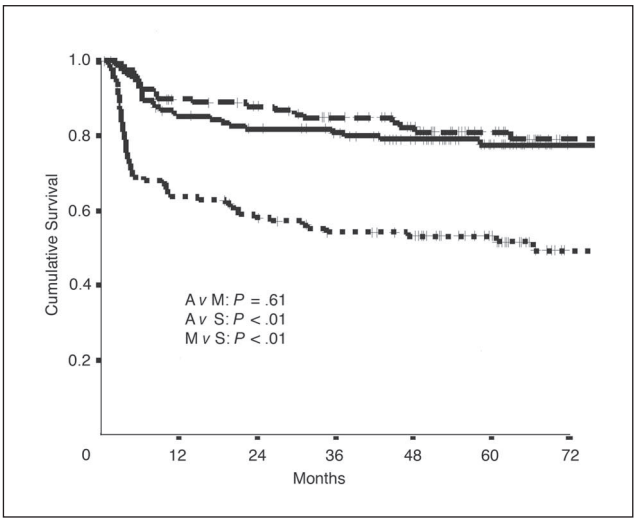

Fig 3. Failure-free survival by treatment arm. Continuous line: doxorubicin, bleomycin, vinblastine, and dacarbazine (A; 126 patients); dashed line: mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (M; 113 patients); dotted line: doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (S; 115 patients).

basic purpose of this trial, which was started 8 years ago, was to evaluate which chemotherapy regimen would be best associated with a decidedly reduced radiotherapy program, mainly guided by the presence of an initial bulky mass, as one of the most crucial prognostic factors, or by the response recorded to the preceding chemotherapy. Another basic requirement was that the chemotherapy should last no more than 6 months, abandoning any extension to the eight, nine, or even 12 cycles previously administered.

The choice of ABVD as the reference chemotherapy regimen for advanced HL was mandatory given the huge amount of data confirming the relative best efficacy to toxicity ratio of this regimen.[1,5] We chose to explore the ability of the Stanford V regimen to remain effective in combination with a lower dose of radiation therapy than

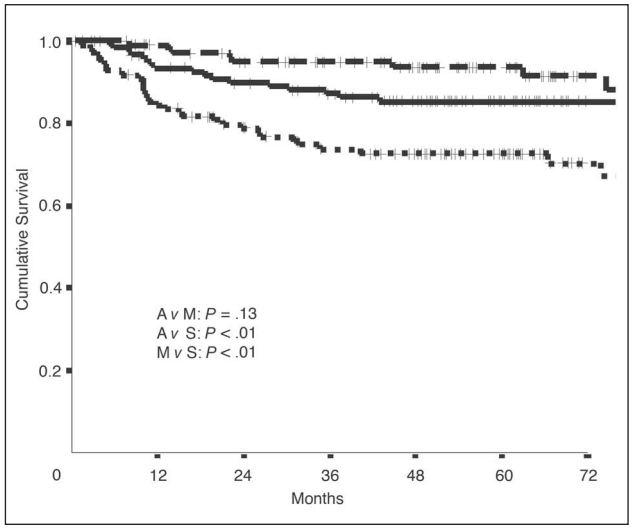

Fig 2. Freedom from progression by treatment arm. Continuous line: doxorubicin, bleomycin, vinblastine, and dacarbazine (A; 126 patients); dashed line: mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (M; 113 patients); dotted line: doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (S; 115 patients).

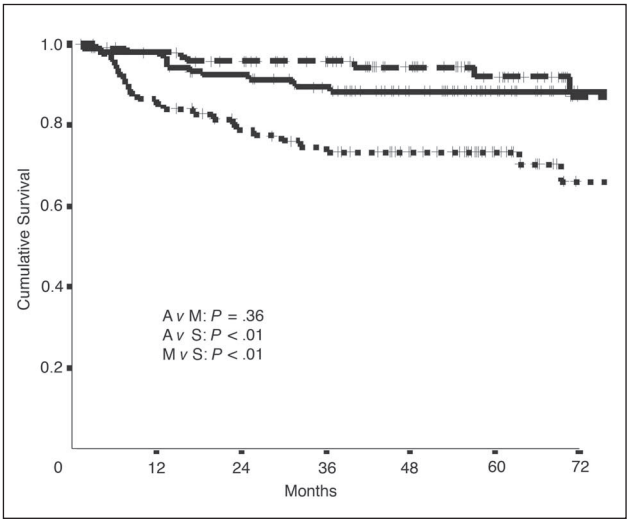

Fig 4. Relapse-free survival of complete responders. Continuous line: doxorubicin, bleomycin, vinblastine, and dacarbazine (A; 109 patients); dashed line: mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (M; 100 patients); dotted line: doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (S; 81 patients).

that planned in the original protocol by virtue of its innovative chemotherapeutic schedule. In fact, the therapeutic scheme designed by Horning et al[9] and Bartlett et al[16] provides weekly exposure to active drugs, alternating myelotoxic and nonmyelotoxic agents, for a total of 12 weeks, with the goal of testing the theory of Goldie et al,[28] which predicts better results if effective agents are introduced early in the course of treatment rather than sequentially. The methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin regimen, with similar frequent drug administration over a relatively short time, has been demonstrated to be effective in the treatment of large-cell non-HL.[29]

The MOPPEBVCAD chemotherapy regimen was born from a modification of the alternating lomustine, doxorubicin, and vindesine/MOPP/ABV program of Straus et al[30] through hybridization of the drugs and shortening of the duration of the whole regimen, resulting in a feasible dose intensification of approximately 30% to 40% compared with that of the original alternating schedule. In 1987, this rationale seemed to comply well with the hypothesis of Goldie et al.[28] Results were interesting (a CR rate of 94%; use of radiotherapy in only 32% of patients, nearly all of whom were in CR or CRu after chemotherapy; 5-year OS and FFS of 89% and 78%, respectively).[11] Now, according to the more recent theoretical model of Hasenclever et al[31] regarding the relationship between effective dose and cure rate, escalating doses within the same treatment duration seem to be better than shortening cycle intervals while maintaining the same dose size of each drug. The recent experiences of the German Hodgkin's Study Group with escalated BEACOPP[7] seem to confirm this hypothesis. From this point of view, the slight difference in disease control observed in this trial between ABVD and MOPPEBVCAD was to be expected. According to the same model, the lower activity demonstrated by the Stanford V regimen would be explained by the lower total effective dose of active drugs caused by the administration of conventional doses in too short a period.

The type of drugs included in the therapeutic combinations probably also plays a crucial but not quantified role in these models, besides the undeniable role of drug dose size, dose-intensity, and total dose. We are not referring to the intensive use of vinca alkaloids in 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 Gruppo Italiano Studio Linfomi trial, published in 2000,[32] demonstrated that lomustine and melphalan are decisive in the efficacy of the combination (or, at least, that they cannot be replaced by cyclophosphamide and etoposide), and this did not contribute to reducing the concern regarding the presence of three alkylating agents and one nitrosourea in the regimen. Actually, the absolute number of second tumors so far recorded in trials with MOPPEBVCAD is not high[11] and is comparable to the number reported after alternated MOPP/ABVD or chlorambucil, vinblastine, procarbazine, and prednisone. This might be because the number of potentially oncogenic drugs used is counterbalanced by their low cumulative absolute doses as well as by the less frequent association of radiotherapy, which, moreover, if administered, is delivered to limited fields and in limited doses.

The last matter of the criteria for associating radiotherapy in the three arms of this trial deserves further examination, particularly because the criteria can be suspected of having determined the less favorable outcomes in the Stanford V arm compared with the previously recorded results in the original series.[9,16,33] In the majority of trials over the last 15 years when intense chemotherapy regimens have been administered, radiotherapy has generally been limited as much as possible and frequently avoided. Both the original protocol with MOPPEBVCAD and most of the trials with six to eight cycles of ABVD in advanced-stage HL adopted radiotherapy as an ancillary measure, and radiotherapy was limited to sites of previous bulky masses or incomplete response to chemotherapy. The Stanford V chemotherapy protocol was originally designed to be followed by consolidating irradiation to a mantle field for bulky mediastinal disease, to spleens with macroscopic nodules, or to nodal sites showing residual radiographic abnormalities after chemotherapy. Because this last condition required extensive irradiation for minimal radiographic alterations, which seldom corresponded to real presence of disease, the protocol was amended 2 years after its introduction. Thereafter, nodal sites were irradiated only in case of initial bulky involvement, defined as diseased sites with a horizontal diameter more than 5 cm. Bulky mediastinal masses were treated with irradiation limited to mediastinum, bilateral hilar and supraclavicular areas, and possible contiguous extralymphatic sites. With these criteria, nearly 90% of patients received irradiation to multiple sites with doses fixed at 36 Gy.

This was the available information on the ongoing Stanford V protocol, together with the results achieved on the first 65 patients, when our trial started at the beginning of 1996. The criteria for irradiation we used in the three arms of this trial were more restrictive than those of the original Stanford protocol (but also more permissive than those in the original MOPPEBVCAD study,[11] in which radiotherapy was administered to only 32% of patients). In the present trial, some degree of discretion was left to clinicians, who had to decide whether to irradiate a patient on the basis of the clinical evaluation of response after two to three cycles of therapy and mainly at the end of chemotherapy. We acknowledge that the time of evaluating both the first and final responses was different for the Stanford V regimen (at weeks 8 and 12, respectively) than for the ABVD and MOPPEBVCAD regimens (weeks 16 and 24, respectively). Moreover, the rather long median time from the conclusion of chemotherapy to the start of radiotherapy might

have influenced the final outcome of the brief Stanford V chemotherapy regimen more than that of the other two longer regimens, although the median intervals between chemotherapy and radiotherapy were similar in all three treatment arms. However, evaluation of the response to the preceding chemotherapy was the necessary step for identifying those patients who might be spared radiotherapy and those patients who had to undergo it. Of course, this decisional step had to be irrespective of the length of the chemotherapy schedules, which were unmodified parts of the original therapeutic combinations compared. We probably must accept that Stanford V chemotherapy, which was originally devised as largely dependent on the subsequent radiotherapy program, is not so effective as to tolerate further, although selective, reduction of the radiotherapy. Limiting the radiotherapy to no more than two sites might also have disadvantaged the patients in the Stanford V arm because of its shortness and lower efficacy.

Moreover, the slightly lower proportion of stage IIB patients with nodular sclerosis histology and mediastinal bulk in the MOPPEBVCAD arm might have resulted in an advantage that outweighed the disadvantage given by a higher number of stage III patients. However, even in a direct comparison of both strategy and results with the original design of the Stanford V, the differences in the criteria addressing the patient to radiotherapy are not substantial and do not seem to have affected the results remarkably. Five patients in the modified Stanford V arm, who were not considered as having bulky nodal disease according to our criteria (diameter $\geq$ 6 cm) but who would have according to the criteria of Horning et al[9] (diameter $\geq$ 5 cm), did not undergo irradiation, but all are in continuous CR after at least 60 months of follow-up. We did not specifically codify for irradiation of the spleen when macroscopically involved, but we did not exclude this strategy, leaving it to be decided along the adopted general criteria. In fact, eight of the nine patients with nodular splenic involvement in the modified Stanford V arm received irradiation to the spleen, and the one patient who did not achieved CR anyway, which still lasts uninterrupted after 58 months. Finally, five CRs, three PRs, and one patient with disease progression were recorded in nine patients who should have received radiotherapy after our modified Stanford V combined program (because of initial bulky mass or CRu or PR after chemotherapy) but did not. These patients may have contributed to lowering the FFS and PFS curves in the Stanford V arm (particularly because two of the complete responders subsequently relapsed and died of the disease). The reasons why clinicians preferred to refer patients directly to salvage chemotherapy rather than radiotherapy were unsatisfactory response evaluated after 8 and 12 weeks of therapy, the difficulty in starting radiotherapy earlier than 6 weeks after the end of chemotherapy, with fear of disease progression during the interval, and persisting signs of disease in more than two anatomic sites that would have required multisite radiation therapy. Other general factors may also have contributed to lower the response to the Stanford V program in this trial compared with the response in the original study. It is well known that various subtle and unintentional but largely unavoidable biases underlie multicenter studies and often impair their results when compared with those from single centers. Moreover, it must be acknowledged that the skill and great experience of the radiation oncologists of Stanford University can hardly be paralleled in any other institutions at present. Finally, the patients' characteristics may also have a bearing because our patients were decidedly older; 6% of the 142 patients in the study by Horning et al[9] were 45 years old or older, whereas 25% of the patients in our Stanford V arm (as in the other arms) of our study were 45 years old or older.

Thus, the conclusions of this study may be summarized as follows. First, when ABVD, Stanford V, and MOPPEBVCAD chemotherapy regimens are used with optional, bulkiness- and/or response-oriented (not adjuvant or consolidation) radiotherapy, both ABVD and MOPPEBVCAD are superior to the modified Stanford V program in terms of response rate, FFS, and PFS, whereas the OS of all the regimens are equivalent because of the use of effective salvage therapies or a balance of different fatal toxicities. Second, with the criteria for irradiation used in this trial, which were more restrictive than the criteria of the original Stanford V program, radiation is less frequently required after MOPPEBVCAD than after ABVD and Stanford V. Third, regarding early toxicity, ABVD is better tolerated than Stanford V 12-week chemotherapy, which, in turn, is better tolerated than MOPPEBVCAD. Fourth, so far, second cancers have only occurred in the trial arms in which alkylating agents were administered. More prolonged follow-up is needed to see whether the higher responses to MOPPEBVCAD will be partially or fully counterbalanced by the incidence of late second cancers. Finally, from the results of this trial and from the comparison with the MOPPEBVCAD and Stanford V chemotherapy regimens, ABVD still seems to offer the best and most reliable balance between efficacy and toxicity.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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