Rapidly Alternating COPP/ABV/IMEP Is Not Superior to Conventional Alternating COPP/ABVD in Combination With Extended-Field Radiotherapy in Intermediate-Stage Hodgkin's Lymphoma: Final Results of the German Hodgkin's Lymphoma Study Group Trial HD5

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Purpose: **To investigate whether treatment results in intermediate-stage Hodgkin's lymphoma can be improved by rapid application of non–cross-resistant drugs, the 10-drug regimen cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), doxorubicin, bleomycin, and vinblastine (ABV), and ifosfamide, methotrexate, etoposide, and prednisone (IMEP), repeated every 6 weeks, was compared with conventional alternating COPP/doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) administered every 8 weeks.**

Patients and Methods: **From January 1988 to January 1993, 996 patients in stage I or II Hodgkin's lymphoma with at least one risk factor (massive mediastinal tumor, massive spleen involvement, extranodal disease, elevated ESR, or more than two lymph node areas involved) and all patients in stage IIIA Hodgkin's lymphoma were randomized to receive two cycles of COPP/ABVD or COPP/ABV/IMEP followed by extended-field radiotherapy.**

Results: **Both regimens produced similar rates for treatment responses (complete remission, 93% *v* 94%), freedom from treatment failure (80% *v* 79%), and overall survival (88% for both regimens) at a median follow-up time of 7 years. Most serious toxicities during chemotherapy were similar in both regimens. However, World Health Organization grade 3 and 4 leukocytopenia occurred significantly more frequently in the COPP/ABV/IMEP arm (53% *v* 44% of patients; *P* = .010). There were no differences in the number of serious infections and toxic deaths during therapy. The number of second malignancies was also the same in both arms (22 each).**

Conclusion: **Alternating COPP/ABVD and rapid alternating COPP/ABV/IMEP in combination with extended-field radiotherapy are equally effective in intermediate-stage Hodgkin's lymphoma and produce excellent long-term treatment results.**

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PATIENTS WITH intermediate-stage (unfavorable early-stage) Hodgkin's lymphoma can be cured with combined chemoradiotherapy. However, the optimal chemotherapy regimen, the number of chemotherapy cycles, the radiotherapy volume, and the dose of radiotherapy is still under debate.

The German Hodgkin's Lymphoma Study Group (GHSG) defines the intermediate stage as pathologic or clinical stage I, II with additional prognostically adverse factors, and all stage IIIA. In our database, 8% to 12% of patients in the intermediate stage treated with standard chemoradiotherapy programs will not achieve a complete remission (CR) after first-line therapy. Additionally, 15% of those achieving a CR subsequently experience relapse. The prognosis of these treatment failures after combined-modality treatment is extremely poor.[1,2]

The efficacy of the standard regimens, such as mechlorethamine, vincristine, procarbazine, and prednisone (MOPP); doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); and MOPP alternating with ABVD, in the treatment of Hodgkin's lymphoma is well documented. A large randomized trial from Cancer and Leukemia Group B in advanced-stage Hodgkin's lymphoma demonstrated that the anthracycline-containing regimens ABVD and MOPP alternated with ABVD were more effective than MOPP alone.[3]

In the late 1970s, Goldie and Coldman[4] presented a mathematic model that related the drug sensitivity of tumors to their spontaneous mutation rate. This model provided the rationale for the development of rapidly alternating non–cross-resistant chemotherapy programs.[5] In an attempt to meet the requirements of the Goldie and Coldman model,

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Klimo and Connors[6] designed a new regimen that consisted of half a cycle of MOPP and half a cycle of ABVD administered within 1 month. Results from a pilot study and the preliminary report from an intergroup trial indicated a high level of efficacy of this hybrid regimen in advanced stages.[7,8]

In the late 1980s, the GHSG designed the rapidly alternating cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), doxorubicin, bleomycin, and vinblastine (ABV), and ifosfamide, methotrexate, etoposide, and prednisone (IMEP) regimen. Compared with the German standard regimen of COPP alternating with ABVD, in which eight drugs were given within 8-week intervals, the COPP/ABV/IMEP regimen combined 10 drugs in 6-week intervals.

In 1989, the GHSG started two randomized multicenter trials for advanced-stage (Hodgkin's disease [HD]6 trial) and intermediate-stage (HD5 trial) Hodgkin's lymphoma to compare the rapidly alternating COPP/ABV/IMEP regimen with the conventional alternating COPP and ABVD regimen. In intermediate-stage patients, two cycles of either chemotherapy regimen were followed by extended-field radiotherapy. Here, we report the results at a median follow-up of 7 years of the multicenter HD5 trial in intermediate-stage Hodgkin's lymphoma.

PATIENTS AND METHODS

Eligibility

This study enrolled patients between 15 and 75 years of age with biopsy-proven Hodgkin's lymphoma. Patients had clinical stage (CS) or pathologic stage (PS) I or II with one or more of the following risk factors: massive mediastinal tumor (≥ one third of the maximum thoracic diameter), massive spleen involvement (diffuse infiltrations or more than five focal lesions), extranodal disease, elevated erythrocyte sedimentation rate (ESR; ≥ 30 mm/h with B symptoms, ≥ 50 mm/h without B symptoms), and more than two lymph node areas involved. In addition, patients with stage IIIA disease were enrolled.

Staging was based on Ann Arbor criteria and resulted from a physical examination; chest radiography; computed tomography (CT) of the chest, abdomen, and pelvis; bone marrow biopsy; and liver biopsy. All patients had a peripheral-blood count and blood chemistry, including ESR, evaluated. According to the protocol instructions, staging laparotomy was performed only in patients with stage CS I and II disease without risk factors who would potentially qualify for a treatment strategy with radiotherapy alone according to a treatment protocol for early stages.

Patients with impaired heart, lung, liver, or kidney function or previous malignant disease were excluded. Each patient provided written informed consent.

Recruitment

Recruitment onto the HD5 trial began in January 1988 and continued until January 1993 at a rate of approximately 200 patients per year. One hundred twenty-nine institutions and oncologic practices, mainly in Germany but also in Switzerland, Italy, and Austria, participated (Appendix 1).

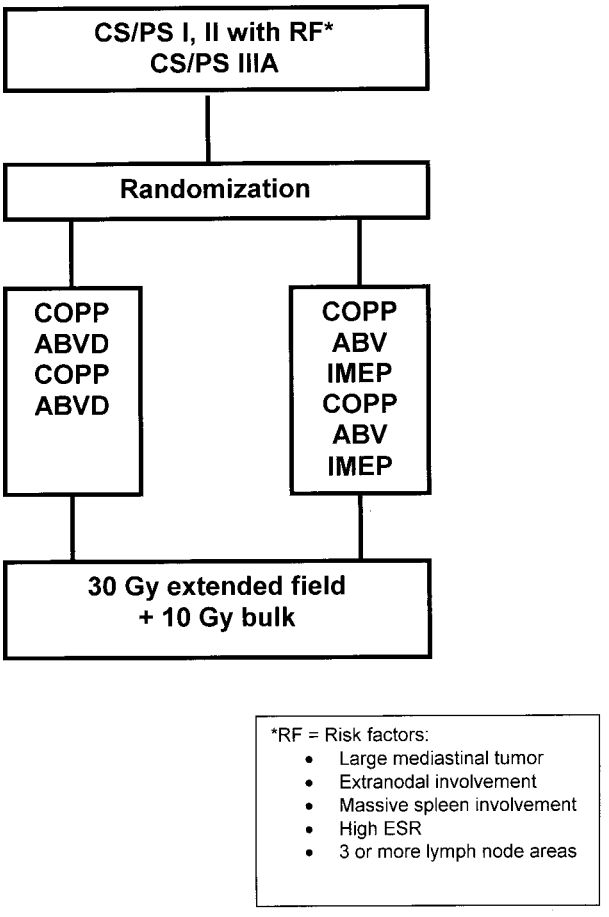

Fig 1. Flow diagram of the HD5 trial.

Pathology Review

Histologic diagnosis was made initially by local pathologists, who were asked to send paraffin-block biopsy samples to a central pathology review panel that involved four leading German lymphoma experts (Appendix 2). The pathology review panel reclassified all biopsy samples. However, registration onto the trial occurred on the basis of the initial diagnosis. Cases with a review diagnosis other than Hodgkin's lymphoma were excluded from analysis. In the absence of a review diagnosis, the initial diagnosis of Hodgkin's lymphoma was deemed sufficient for eligibility.

Treatment

The study design is summarized in Fig 1. Patients were randomly assigned to receive two cycles of alternating COPP/ABVD or rapidly alternating COPP/ABV/IMEP followed by extended-field radiotherapy. The alternating regimen consisted of one full cycle of COPP monthly alternated with one full cycle of ABVD. COPP is identical to standard MOPP except that cyclophosphamide was substituted for mechlorethamine. In the rapidly alternating regimen, all drugs of COPP and ABVD (except dacarbazine) were administered with a modification in dose and time schedule within the first 15 days followed by the IMEP regimen from day 29 to day 35. This 10-drug regimen was

Table 1. Planned Dosage and Schedule of the COPP/ABVD and COPP/ABV/IMEP Regimens

	COPP/ABVD (recycle day 57)			COPP/ABV/IMEP (recycle day 43)		
	mg/m^2	Route	Day	mg/m^2	Route	Day
Cyclophosphamide	650	IV	1, 8	800	IV	1
Vincristine	1.4*	IV	1, 8	1.4*	IV	1
Procarbazine	100	PO	1-14	100	PO	1-10
Prednisone	40	PO	1-14	40	PO	1-15
Doxorubicin	25	IV	29, 43	40	IV	15
Bleomycin	10	IV	29, 43	10	IV	15
Vinblastine	6	IV	29, 43	6	IV	15
Dacarbazine	375	IV	29, 43			
Ifosfamide				1000	IV	29-33
Methotrexate				30	IV	31
Etoposide				100	IV	29-31
Prednisone				40	PO	29-35

Abbreviations: IV, intravenous; PO, oral.

*Maximal 2 mg.

recycled every 6 weeks. The chemotherapy regimens were administered as described in Table 1. The protocol gave detailed instructions as to the amount of dose reduction and postponement of therapy if myelopoietic toxicity occurred.

Thirty-two of the 67 patients recruited from centers in Switzerland received mechlorethamine instead of cyclophosphamide (MOPP instead of COPP), with a standard dose of 6 mg/m^2 in both regimens. These patients were considered eligible for analyses of treatment results but not for analyses of acute toxicities. The treatment results in terms of freedom from treatment failure (FFTF) and overall survival (OS) of the MOPP-treated patients were not different from the COPP patients.

Extended-field radiotherapy began 4 to 8 weeks after the last cycle of chemotherapy in both treatment arms. The total dose was 30 Gy for the extended field, with a boost up to 40 Gy for bulky tumors. Bulky tumor was defined as a tumor mass $\geq$ 5 cm in the maximal diameter measured in CT scans. Doses had to be delivered in 1.8- to 2.0-Gy daily fractions with megavoltage radiation. Extended-field radiotherapy implied the following volumes: supradiaphragmatic involvement: only mantle field, para-aortic spade, and spleen; supradiaphragmatic and subdiaphragmatic involvement: mantle field, inverted-Y field, and spleen; and subdiaphragmatic involvement: only T field, inverted-Y field, and spleen. A break of 2 to 4 weeks between supradiaphragmatic and infradiaphragmatic treatment was recommended. The radiation volume of a massive mediastinal mass encompassed the original volume up to a 16-Gy total dose. Reduced volumes were recommended for subsequent fractions.

Response Assessment and Follow-up

The success of treatment was determined by restaging immediately after four cycles of chemotherapy and 4 to 8 weeks after radiotherapy. Restaging consisted of a control and careful documentation of all initial disease manifestations by adequate clinical methods, including a physical examination; complete blood cell count; blood chemistry; and CT of the chest, abdomen, and pelvis. CR was defined as the disappearance of all disease manifestations. Partial remission was defined as a reduction in all disease manifestations by at least 50% compared with the initial involvement. Patients with questionable persisting disease were classified as partial responders, which also included the status of uncertain CR with residual mass.

Follow-up examinations, including medical history and physical examination, complete blood cell count and blood chemistry, chest x-ray, and abdominal ultrasound, were performed within the first 2 years in 3-month intervals, at years 3 and 4 in 4-month intervals, and from year 5 onward in 6-month intervals.

Statistical Analysis

All eligible patients (N = 975) were included in the analysis of overall results, whereas only assessable patients (n = 973) were included in comparisons of treatment. Survival analyses used the Kaplan-Meier method. The significance of comparisons of treatment was calculated with the log-rank test. FFTF was defined as the time from randomization to the first of the following events: death, progressive disease, non-CR status at the end of the treatment, or relapse. Relapse-free survival (RFS) was defined as the time from documented CR status to the occurrence of a relapse. OS time was measured from randomization until death from any cause. Comparisons of treatment groups were performed according to intention to treat for survival analysis, although comparisons of treatment duration were carried out only for patients who had received the intended treatment.

A univariate analysis was used to assess prognostic parameters for their impact on Hodgkin's-specific FFTF, including only events related to Hodgkin's lymphoma. The parameters tested included sex, age (less than 45 years *v* 45 years and above), stage of the disease (I-IIA *v* IIB-IIIA), bulky disease, and the risk factors large mediastinal mass, extranodal involvement, massive splenic involvement, more than two lymph node areas involved, and elevated ESR. Additionally, Cox regression using the Wald statistic was performed to compare the influence of the prognostic parameters in a multivariate analysis.

RESULTS

Patient Characteristics

Between January 1988 and January 1993, 996 patients were randomized onto the study. Of these, 21 patients were not eligible for the following reasons: concurrent disease before the start of therapy (n = 8), improper staging (n = 1), wrong therapy (n = 3), and patient refusal to provide informed consent (n = 1). Additionally, two patients were not assessable for arm comparison as a result of lack of documentation (n = 1) or refusal of any therapy. These two patients were considered for overall results but were not included in arm comparison. Eight patients were not eligible because the pathology review panel revealed diagnoses other than Hodgkin's lymphoma: non-Hodgkin's lymphoma in five cases and nonmalignant lesions in three cases. Of the 973 assessable patients, histologic diagnosis was re-evaluated in 651 cases (67%). The remaining specimens were not submitted.

Of the 973 assessable patients, 487 patients were randomly assigned to receive the alternating COPP/ABVD regimen, and 486 patients were assigned to receive the rapidly alternating COPP/ABV/IMEP regimen. The clinical characteristics of the 973 patients suitable for arm comparison are listed in Table 2. Age, sex, histology subtype, stage,

Table 2. Patient Characteristics

	COPP/ABVD (n = 487)		COPP/ABV/IMEP (n = 486)	
	No.	%	No.	%
Age, years				
Median	31		31	
Range	16-74		16-72	
Sex, male	266	54	253	52
Stage (CS/PS)				
IA	14	3	17	4
IB	17	3	15	3
IIA	181	37	192	40
IIB	133	27	123	25
IIIA	142	29	139	29
B symptoms present	150	31	138	28
Bulky disease	247	51	246	51
Staging laparotomy	92	19	82	17
Histologic subtype*				
LP	6	2	15	5
NS	222	68	209	65
MC	49	15	45	14
LD	2	1	4	1
ER	10	3	13	4
Unclassified	28	8	25	8
HD uncertain	12	4	11	3
Risk factor				
Large mediastinal mass	114	23	125	26
Extranodal involvement	57	12	56	12
Massive spleen involvement	43	9	25	5
Two or more lymph node areas	313	64	304	63
High ESR	247	51	231	47

Abbreviations: LP, lymphocyte-predominant disease; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte-depleted disease; ER, epitheloid cell-rich disease.

*The histologic subtype was reviewed in 68% cases for the COPP/ABVD arm and in 66% cases for the COPP/ABV/IMEP arm; these percentages refer to reviewed cases only.

B symptoms, bulky disease, and incidence of the risk factors were well balanced between the two arms of the trial.

Response to Treatment

Response rates did not differ significantly between the two arms, as summarized in Table 3. CR rates were 45% for the COPP/ABVD arm and 41% for COPP/ABV/IMEP arm after chemotherapy and increased after the completion of therapy with extended-field irradiation to 93% and 94%, respectively. Two patients died during therapy, one in each treatment arm.

FFTF and RFS

Analysis of the FFTF rates was conducted at a median follow-up of 86 months. For the entire cohort of 975 eligible patients, the 7-year FFTF rate was 79% (95% confidence interval, 76.39% to 81.61%), with no difference between the COPP/ABVD arm (80%) and the COPP/ABV/IMEP arm (79%) (Fig 2). Overall, 99 events were registered in the COPP/ABVD arm, and 107 events were registered in the COPP/ABV/IMEP arm (Table 4).

At the time of this analysis, 94 patients have experienced relapse (39 in the COPP/ABVD arm and 55 in the COPP/ABV/IMEP arm). The 7-year RFS rate for the COPP/ABVD arm was 91%, compared with 87% in the COPP/ABV/IMEP arm (no significant difference).

Table 3. Response to Treatment After Completion of Chemotherapy and Radiotherapy

	COPP/ABVD (n = 487)		COPP/ABV/IMEP (n = 486)	
	After CT (%)	After CT + RT (%)	After CT (%)	After CT + RT (%)
CR	45	93	41	94
PR	51	2	54	2
NC	< 1	< 1	< 1	—
PRO	< 1	4	1	3
Death during therapy	—	< 1	—	< 1
Unknown	2	< 1	3	1

Abbreviations: CT, chemotherapy; RT, radiotherapy.

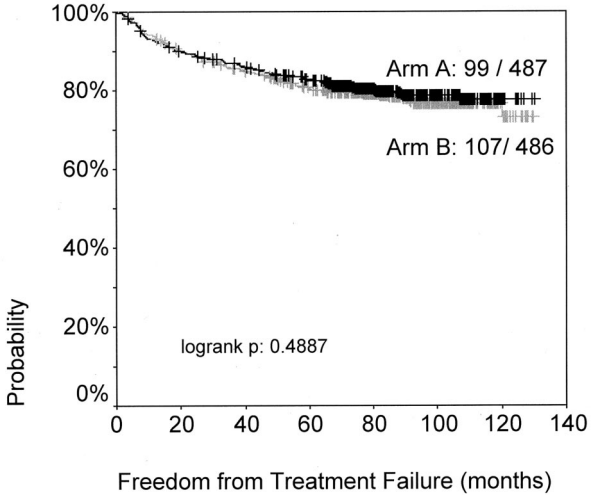

Fig 2. FFTF for arm A (COPP/ABVD) versus arm B (COPP/ABV/IMEP).

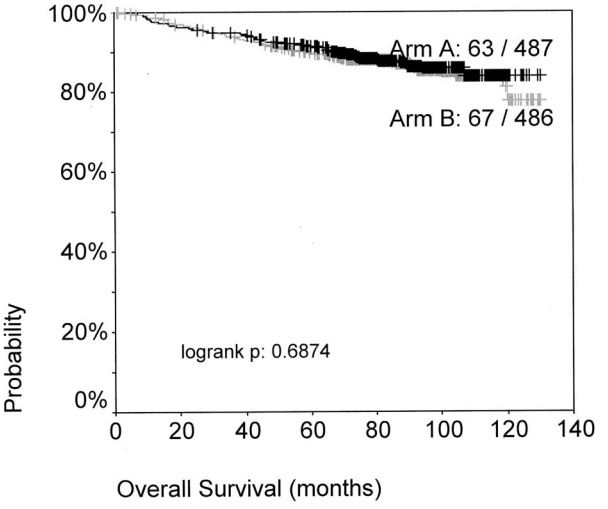

Fig 3. OS for arm A (COPP/ABVD) versus arm B (COPP/ABV/IMEP).

In the univariate test, only extranodal involvement (P = .015) and stage of disease (P = .020) showed a significant impact, and age (P = .059) showed a borderline significant impact on Hodgkin's-specific FFTF. These were also the only significant parameters that remained in the Cox regression model. Additionally, extranodal involvement was associated with a significantly worse CR rate in each treatment arm (COPP/ABVD arm, 86% *v* 94%; P = .011; COPP/ABV/IMEP arm, 82% *v* 96%; $P < .001$).

OS

At the time of this analysis a total of 130 patients had died, 63 in the COPP/ABVD arm and 67 in the COPP/ABV/IMEP arm. The OS rate at 7 years was 88% (95% confidence interval, 85.86% to 90.14%), with no difference between both treatment arms (Fig 3). Table 5 lists the causes of deaths. The majority of deaths were disease-related, followed by deaths from secondary malignancies (no differences between the treatment arms). A relatively large number of cardiac-related deaths in the COPP/ABVD arm compared with the COPP/ABV/IMEP arm (11 *v* two deaths) was documented.

Treatment Delivery

Only 14 patients received less than the projected two cycles of chemotherapy, 11 patients in the COPP/ABVD arm and three patients in the COPP/ABV/IMEP arm. The reasons for discontinuation included progressive disease (n = 5), serious toxicity (n = 2), concurrent disease (n = 1), and patient wish (n = 6). The median duration of chemotherapy (time from the first day of the first cycle to the last day of the second cycle) was 15.1 weeks in the COPP/ABVD arm (14.1 weeks planned) and 12.6 weeks in the COPP/ABV/IMEP arm (11.0 weeks planned).

The dose-intensity for each drug is summarized in Table 6. A higher dose-intensity was achieved with the conventional alternating COPP/ABVD for all comparable drugs. In

Table 4. Events for FFTF

Event	COPP/ABVD (n = 487)	COPP/ABV/IMEP (n = 486)
PR	11	8
NC	1	—
PRO	21	14
Death	26	25
Relapse	39	55
Unknown	1	5
Overall	99	107

Table 5. Causes of Deaths

	COPP/ABVD (n = 63)	COPP/ABV/IMEP (n = 67)
Hodgkin's lymphoma		
No.	26	30
%	41	45
Excessive toxicity after first-line treatment	4	2
Excessive toxicity after second-line treatment	3	6
Secondary neoplasia	14	12
Cardiac disease	11	2
Other diseases	1	6
Accident	—	2
Unknown	4	7

Table 6. Median Dose-Intensity of Chemotherapy

Drug	COPP/ABVD		COPP/ABV/IMEP	
	mg/m2/wk	Planned (%)	mg/m2/wk	Planned (%)
Cyclophosphamide	170.1	92	126.0	87
Vincristine	0.29	72	0.18	71
Procarbazine	177.7	90	154.3	85
Prednisone	73.9	93	138.1	86
Doxorubicin	6.5	92	6.3	87
Bleomycin	2.5	88	1.54	85
Vinblastine	1.5	89	0.9	86
Dacarbazine	96.0	90	—	—
Ifosfamide	—	—	789.4	87
Methotrexate	—	—	4.74	87
Etoposide	—	—	47.6	87

addition, the median relative dose-intensity (percent of the planned dose-intensity) was higher in the COPP/ABVD arm than in the COPP/ABV/IMEP arm. Thus, the actual delivered dose and the ability to deliver the planned dose was higher in the COPP/ABVD arm (Table 6).

Forty-nine patients did not receive or complete the assigned extended-field radiotherapy, 27 patients of the COPP/ABVD arm and 22 patients of the COPP/ABV/IMEP arm. The reasons did not differ by treatment arm and included progressive disease (n = 18), excessive toxicity (n = 6), patient wish (n = 10), protocol violation (n = 13), and unknown (n = 2). The number of irradiated lymph node regions was equally distributed in both treatment arms.

Toxicity and Second Malignancies

The frequencies of serious or life-threatening toxicities during chemotherapy were similar in both treatment arms (Table 7). However, World Health Organization grade 3 and 4 leukocytopenia was encountered significantly more often in the COPP/ABV/IMEP arm (53% *v* 44%; $P = .010$). However, there were no significant differences in the number of World Health Organization grade 3 and 4 infections or in the number of overall toxic deaths during therapy.

Table 7. Percentage of Patients With Acute Toxicity (WHO grade 3 or 4) During Chemotherapy

Toxicity	COPP/ABVD (n = 422)	COPP/ABV/IMEP (n = 423)	*P*
Leukocytopenia	44	53	.010
Thrombocytopenia	0.2	1	
Anemia	0.2	0.5	
Infection	2	3	
Cardiac	0.5	0.5	
Pulmonary	0.5	0.5	
Emesis	25	11	< .001
Alopecia	22	31	.002

Abbreviation: WHO, World Health Organization.

Comparing the serious but not life-threatening toxicities during chemotherapy, alopecia was more frequent (31% *v* 22%; $P = .002$) and emesis was less frequent (11 *v* 25%; $P < .001$) in the COPP/ABV/IMEP arm. Overall, 44 second malignancies were documented, with a median follow-up time of 86 months (22 in each treatment arm). In 26 patients, the second tumor represented the cause of death. Of the 44 patients with a second malignancy, nine patients developed acute nonlymphocytic leukemia, 10 developed non-Hodgkin's lymphoma, and 25 developed solid tumors.

DISCUSSION

The following findings emerged from this study: (1) Treatment results in patients with intermediate-stage Hodgkin's lymphoma administered the multiagent chemotherapy regimens COPP/ABVD and COPP/ABV/IMEP followed by extended-field radiotherapy were excellent. The 7-year rates for FFTF and OS were 79% and 88%, respectively, showing no significant differences between the two arms (80 *v* 79%, 88 *v* 88%). (2) The rapidly alternating COPP/ABV/IMEP failed to improve the treatment results in comparison with the standard alternating COPP/ABVD. (3) Acute toxicity profiles of both regimens are comparable and moderate. (4) The most frequent reason for death was Hodgkin's lymphoma. However, a substantial number of patients died as a result of secondary malignancies. In addition, a higher proportion of patients died from cardiac disease, with more cardiac deaths in the standard COPP/ABVD treatment arm than in the rapidly alternating COPP/ABV/IMEP arm.

Patients with Hodgkin's lymphoma have traditionally been divided into three prognostic groups. The most important factor used to allocate a patient to one of these groups is the stage of disease. The presence of further prognostic factors was often used to assign stage IIIA or IIB patients to the advanced-stage group. Among the remaining patients with early-stage Hodgkin's lymphoma (CS/PS I and II), an unfavorable subgroup (intermediate stages) was often defined to select patients for combined-modality treatment. Such adverse prognostic factors varied between trial groups. Mainly on the basis of the results of early European Organization for Research and Treatment of Cancer and Stanford trials, the GHSG defined CS I and II patients as being in the intermediate stage if they had at least one of the following adverse factors: large mediastinal mass, three or more involved lymph node areas, elevated ESR, extranodal involvement, and massive splenic involvement.[9]

It has generally become the procedure of choice to treat intermediate-stage Hodgkin's lymphoma patients with combined chemoradiotherapy. However, the optimal chemotherapy regimen, the number of chemotherapy cycles, the

field size, and the dosage of radiotherapy within these fields are the subjects of debate.

The first combined-modality trial to test MOPP versus ABVD in intermediate-stage patients was the Milan study, conducted between 1974 and 1982, which used split-course treatment (three cycles of chemotherapy before and after subtotal nodal irradiation). This study showed no significant difference in freedom from disease progression.[10] However, in the European Organization for Research and Treatment of Cancer H6U trial (1982 to 1988) that compared split-course MOPP and ABVD, the 10-year survival was equivalent in both arms, but the FFTF rate was significantly higher with ABVD than with MOPP.[11] On the basis of these results and other trials in advanced disease,[3] anthracycline-containing regimens (ABVD and alternating MOPP and ABVD) have become the standard regimen for patients with intermediate Hodgkin's lymphoma. Nevertheless, approximately 5% of those patients will suffer from progressive disease while on therapy, and another 15% will relapse within the following 5 years.[2]

Following the Goldie-Coldman hypothesis, the reason for the failure of chemotherapy is the persistence of sensitive tumor cells (insufficient treatment) or the persistence of resistant tumor cells (ineffective treatment). This hypothesis led to a hybridization of some alternating regimens, which was accomplished by administering all of the drugs used in each cycle. The result is a rapid sequence of drug exposure.

To further assess the possible advantage of rapidly alternating hybrid protocols, the GHSG conducted the randomized prospective trial HD5, which compared COPP/ABV/IMEP with the standard COPP/ABVD regimen. In the trial reported in the present article, 973 eligible patients in the intermediate stage from 129 centers were randomized to receive COPP/ABVD (n = 487) or COPP/ABV/IMEP (n = 486) followed by extended-field radiation in both treatment arms. Both regimens produced similar response, OS, and FFTF rates.

To our knowledge, this is the first randomized trial in intermediate-stage Hodgkin's lymphoma that aimed to improve treatment results by introducing a rapidly alternating or hybrid chemotherapy protocol. Interestingly, several trials that compared alternating conventional chemotherapy regimens with hybrid regimens in advanced-stage Hodgkin's lymphoma have been reported. Both large randomized trials from the Milan group and National Cancer Institute of Canada that compared alternating MOPP/ABVD with hybrid MOPP/ABV found similar outcomes for the two chemotherapy regimens.[12,13] A large intergroup trial from the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and Southwest Oncology Group that compared sequential MOPP/ABVD with hybrid MOPP/ABV in advanced Hodgkin's lymphoma revealed superior results for the hybrid regimen. In contrast to the alternating MOPP/ABVD regimen of the Milan and Canada groups, patients in the sequential MOPP/ABVD arm initially received six to eight cycles of MOPP, followed by three cycles of ABVD. It is remarkable that the hybrid arm was associated with a lower incidence of acute leukemia or myelodysplasia compared with the sequential arm.[14] In contrast, a second intergroup trial that compared the MOPP/ABV hybrid with ABVD alone was closed early because of excessive treatment-related deaths and second malignancies in the hybrid regimen. CR, failure-free survival, and OS rates at 3 years revealed no statistically significant differences.[15] At the Memorial Sloan-Kettering Cancer Center, the 10-drug regimen lomustine, melphalan, and vindesine (CAD)/MOPP/ABV was introduced and compared with MOPP/ABVD in advanced stages. Corresponding to the results with COPP/ABV/IMEP, CAD/MOPP/ABV failed to improve treatment results, but myelosuppression was more frequent, and nausea and vomiting were less frequent with CAD/MOPP/ABV.[16]

With the advent of hematopoietic growth factors, an alternative strategy to possibly improve treatment results has been evaluated that was based on dose intensification.[17,18] The Stanford V regimen administered for 12 weeks to patients with bulky or advanced-stage Hodgkin's lymphoma seems interesting within the context of increased dose-intensity. Within this regimen, myelosuppressive and nonmyelosuppressive drugs were alternated weekly, with the support of granulocyte colony-stimulating factor. A preliminary report of a phase II study that used Stanford V combined with irradiation to initially bulky disease or residual radiographic abnormalities revealed excellent results in CS II patients with bulky mediastinal disease. At 2 years of median follow-up, the failure-free survival rate was 100% for the 21 patients in stage II bulky disease.[19]

The GHSG developed the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen, which encompasses two main dose-intensification strategies: dose escalation of the putatively most important drugs and time intensification accomplished by shortening the respective chemotherapy cycles. Within the escalated BEACOPP variant, the doses of cyclophosphamide, etoposide, and doxorubicin escalated granulocyte colony-stimulating factor support to 192%, 200%, and 140% of the baseline variant, respectively.[20]

A randomized comparison of the BEACOPP regimen, administered in a baseline dose and in an escalated-dose version, with the COPP/ABVD regimen in advanced-stage Hodgkin's lymphoma revealed superior results for the

BEACOPP variants with respect to disease progression, FFTF, and OS rates.[21,22] Thus, the time-intensified and dose-intensified BEACOPP and the Stanford V regimens seemed to approach more closely the optimal strategy suggested by the Goldie-Coldman hypothesis.

The impact of dose-intensity on treatment results might be the reason why the COPP/ABV/IMEP regimen failed to improve the treatment results in the present study. Comparing the dose-intensities (mg/m^2/wk) of both regimens, the conventional COPP/ABVD achieved a higher dose-intensity for all comparable drugs as compared with the rapidly alternating COPP/ABV/IMEP.

In our trial, second malignancy was a frequent reason for death (n = 26). Second malignancies occurred in similar numbers on both treatment arms (22 in each arm). However, it is too early to give a final judgment on the fatal role of second malignancies because the risk of death from second cancers increases with time after treatment.[23]

It is remarkable that a substantial proportion of patients died because of cardiac diseases, with more cardiac deaths in the standard COPP/ABVD treatment arm (n = 11) than in the rapidly alternating COPP/ABV/IMEP arm (n = 2). Although this finding can not be explained conclusively, one possible reason could be the higher dose of the cardiotoxic drug doxorubicin in the COPP/ABVD arm (total dose, 100 mg/m^2 *v* 80 mg/m^2) in combination with the extended-field radiotherapy. However, the critically cumulative dose of doxorubicin of greater than 450 mg/m^2 was not reached in either treatment arm.[24]

The significant impact of extranodal involvement and stage, categorized as I to IIA versus IIB to IIIA in the present study, agreed with the results of Franklin et al,[25] which showed worse disease-free survival for patients with stages IIB to IIIA and early-stage patients with extranodal involvement. It supports the decision to further treat patients with stages IIB to IIIA and risk factors (large mediastinal mass and extranodal involvement) in trials for advanced stages.

As compared with other trials of international Hodgkin's lymphoma study groups,[26-28] treatment results achieved with two cycles COPP/ABVD or COPP/ABV/IMEP followed by extended-field radiation in patients with intermediate-stage Hodgkin's lymphoma were excellent, with an FFTF rate of 79% and an OS rate of 88% after 7 years. Thus, the subsequent trials of the GHSG for patients with intermediate-stage Hodgkin's lymphoma (HD8 and HD11) were aimed at reducing long-term toxicities while maintaining the excellent tumor control rates. The HD8 trial posed the question of radiation field size. Patients were randomized to receive involved-field versus extended-field radiotherapy after two cycles of alternating COPP/ABVD. A first interim analysis of this trial shows that reduction of radiation to the involved field is possible without worsening the treatment results.[29] However, the optimal chemotherapy regimen is still under debate. The GHSG will now favor ABVD alone as the standard regimen instead of COPP alternating with ABVD. ABVD alone was proven to be effective in advanced stages without inducing sterility or secondary leukemias.[3,30,31] With respect to the encouraging results of Stanford V and BEACOPP in advanced stages, it will be of the utmost interest to test these regimens in patients with intermediate-stage disease. In the ongoing HD11 trial, the GHSG compares ABVD with BEACOPP in a baseline dose variant combined with involved-field radiotherapy (30 Gy *v* 20 Gy). In the United States, an intergroup trial was initiated to compare the ABVD regimen with Stanford V.

In conclusion, the rapid alternating COPP/ABV/IMEP failed to improve treatment results in intermediate-stage Hodgkin's lymphoma. Current trials will focus on modern dose-intensified chemotherapy regimens (Stanford V and BEACOPP) in combination with low-dose and small-volume radiotherapy to define the best treatment strategy.

APPENDIX

Appendices 1 and 2 are available online at www.jco.org.

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