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BEACOPP, a New Dose-Escalated and Accelerated Regimen, Is at Least as Effective as COPP/ABVD in Patients With Advanced-Stage Hodgkin's Lymphoma: Interim Report From a Trial of the German Hodgkin's Lymphoma Study Group

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Purpose: **The HD9 trial aims to evaluate whether moderate dose escalation and/or acceleration of standard polychemotherapy is beneficial for advanced-stage Hodgkin's disease (HD). Two variants of a novel bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) scheme (standard and escalated dose) are compared with cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).**

Patients and Methods: **The randomized, three-arm trial recruited patients in stages IIB and IIIA with risk factors and stages IIIB and IV. BEACOPP in baseline dose contains all drug dosages of COPP/ABVD (except vincristine and procarbazine) rearranged in a shorter, 3-week cycle. Escalated BEACOPP uses higher doses of cyclophosphamide, doxorubicin, and etoposide with granulocyte colony-stimulating factor (G-CSF) support. After eight chemotherapy cycles, initial bulky and residual disease is irradiated. The trial is monitored and analyzed by means of a sequential strategy.**

Results: **An interim analysis with 505 assessable patients and a median follow-up of 23 months showed a significant inferiority (according to sequential monitoring strategy) of the COPP/ABVD regimen in progression rate and freedom from treatment failure (FFTF) compared with the pooled results of both BEACOPP variants. The 24-month FFTF rate was 75% for COPP/ABVD and 84% for BEACOPP pooled (P = .034). There was 12% progressive disease with COPP/ABVD and 6% with BEACOPP pooled. Differences in survival were not significant in sequential analysis. The acute toxicity of baseline BEACOPP resembled that of COPP/ABVD; escalated BEACOPP showed increased but manageable hematologic toxicity.**

Conclusion: **Combined with local irradiation, BEACOPP in one or both variants shows superior disease control compared with COPP/ABVD, with acceptable acute toxicity. Further follow-up is required to assess the effect of dosage and the effect on survival and late toxicities.**

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TREATMENT RESULTS in advanced-stage adult Hodgkin's disease (HD) have not perceptibly improved since the introduction of the chemotherapy regimens mustargen, vincristine, procarbazine, and prednisone (MOPP) in 1964 and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in 1975.[1-4] Despite several trials that investigated rearrangements of drug schedule in new hybrid protocols,[5-8] no major reduction in the rate of progressive disease or relapses was achieved.

An alternative strategy for an improvement in results, the increase of dose and/or dose-intensity of cytostatics, has been discussed by De Vita et al[9] and Linch,[10] but very few randomized clinical trials have compared standard with moderately escalated variants of the same regimen.[11] The German Hodgkin's Lymphoma Study Group (GHSG) evaluated this strategy in preparation for the HD9 trial that used mathematical modeling methods and two successive phase II studies. Both the increase of total dose and acceleration of the administration schedule have the potential to increase efficacy. High-dose escalation would only be justifiable for a subgroup of advanced-stage patients with very poor prognosis, but no prognostic factors were available at that time that could identify patients with a prognosis of, for example, a less than 40% disease-free rate.[12,13] Therefore, the strategy considered was a moderate dose escalation for all advanced-stage patients.

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To quantify the relationship between dose, schedule, and efficacy, a classic model for the effect of chemotherapy on tumor was used.[14] The model assumes that the chemotherapy courses produce instantaneous, additive reductions in tumor load and that the tumor grows exponentially in the intervals between courses. The distribution of the model parameters for reduction of tumor load and rate of tumor regrowth was statistically fitted to the therapy and follow-up data of more than 700 patients in the previous GHSG trials for advanced stages.[15] A 30% average relative dose increase was predicted to lead to an 11% improvement in long-term (Hodgkin's-specific) cure rate, which could be adequately measured by a large comparative clinical trial. A 25% acceleration of the schedule, which corresponded to a cycle of 3 instead of 4 weeks, had a predicted increase in efficacy of only 3%.

Since its inception in 1978, the GHSG has used the alternating polychemotherapy cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD for intermediate and advanced stages.[16] The promising strategy of dose escalation faced the problem of increased toxicity and consequent delays between courses. The availability of the hematopoietic growth factor granulocyte colony-stimulating factor (G-CSF) offered the capability to keep myelotoxicities within acceptable limits despite increased doses of those drugs with myelotoxic main side effects. To allow effective G-CSF administration, our previous standard COPP/ABVD regimen was rearranged so that the major myelotoxic substances cyclophosphamide, doxorubicin, and (newly introduced) etoposide were administered days 1 to 3, which permitted administration of G-CSF from day 8 onward after the termination of procarbazine administration. This scheme allowed a shorter cycle of 3 instead of 4 weeks. The addition of etoposide was accompanied by the removal of vinblastine and dacarbazine. In this new regimen, BEACOPP, the effective and chiefly myelotoxic drugs cyclophosphamide, doxorubicin, and etoposide were considered for dose escalation.

A phase II study of 30 advanced-stage HD patients with eight cycles of chemotherapy proved the feasibility and safety of the BEACOPP regimen without dose escalation (baseline) and already suggested that it was highly effective.[17] Starting in 1992, the feasibility of dose escalation of cyclophosphamide, doxorubicin, and etoposide using G-CSF support was investigated in a dose-finding study that included 60 patients.[18] Using the criterion that predefined moderate hematologic or other toxicities (ie, neutropenia < 1,000/μL for more than 4 days, thrombopenia < 50,000/μL once, other World Health Organization [WHO] grade IV toxicity) should not occur in more than 33% of the cycles, maximum acceptable target doses were estimated to be 190% of baseline for cyclophosphamide and 200% for etoposide, whereas doxorubicin was fixed at 140% (to avoid cardiac problems), and all other substances were kept at baseline dose. Considering toxicity-related dose reductions for individual patients, average doses of 145% of baseline target for cyclophosphamide and 150% of baseline target for etoposide were actually administered when these target levels were applied. Again, treatment results were promising with a complete remission (CR) rate of 93% and a current freedom from treatment failure (FFTF) rate of 90% at 24 months.

The HD9 trial was planned to detect and measure the increase in efficacy (if any) caused by dose escalation and acceleration of schedule using a three-arm randomized controlled trial in a multicenter setting that compared baseline and escalated BEACOPP with the classic regimen COPP/ABVD (Fig 1).

PATIENTS AND METHODS

Recruitment

Recruitment onto the HD9 trial began in February 1993 and continued until March 1998 at a rate of approximately 200 patients per year. Two hundred fifty-seven institutions and oncologic practices, mainly in Germany but also in Switzerland (Swiss Institute for Applied Cancer Research), Austria, and the Czech Republic participated. We report here an interim analysis performed on patients assessable in April 1997, at which time 909 patients had been randomized to treatment.

Eligibility

Patients eligible for HD9 have histologically proven untreated HD and are aged between 16 and 65 years, with stages IIB and IIIA disease and at least one risk factor for stages IIIB and IV disease. Laparotomy was optional. The risk factors for stage IIB patients are large mediastinal mass (more than one third of the maximum thoracic diameter), E stage, and massive splenic involvement (with diffuse infiltrations or more than five focal lesions). For stage IIIA patients, the two extra factors of elevated erythrocyte sedimentation rate (> 50 mm/hr asymptomatic, > 30 mm/hr with B symptoms) and three or more affected lymph node areas were also recognized. Biopsy material was reviewed by a panel of four expert pathologists,[19] and randomization was cancelled for all cases in which the initial diagnosis of HD was refuted and for all cases of composite lymphoma. Lack of written informed consent, malignant disease within the last 5 years, or severe impairment of heart, lung, or liver function were criteria for exclusion.

Staging

Stage of disease was determined according to the Ann Arbor classification.[20] Staging included medical history, physical examination, unilateral bone marrow biopsy, chest computed tomographic (CT) scan and radiograph, abdominal CT scan and ultrasound, isotopic bone scan, and laboratory tests. Liver biopsy under sonographic or laparoscopic control was also specified, but was actually performed in only 74% of the assessable cases. Bipedal lymphangiography and staging laparotomy were optional.

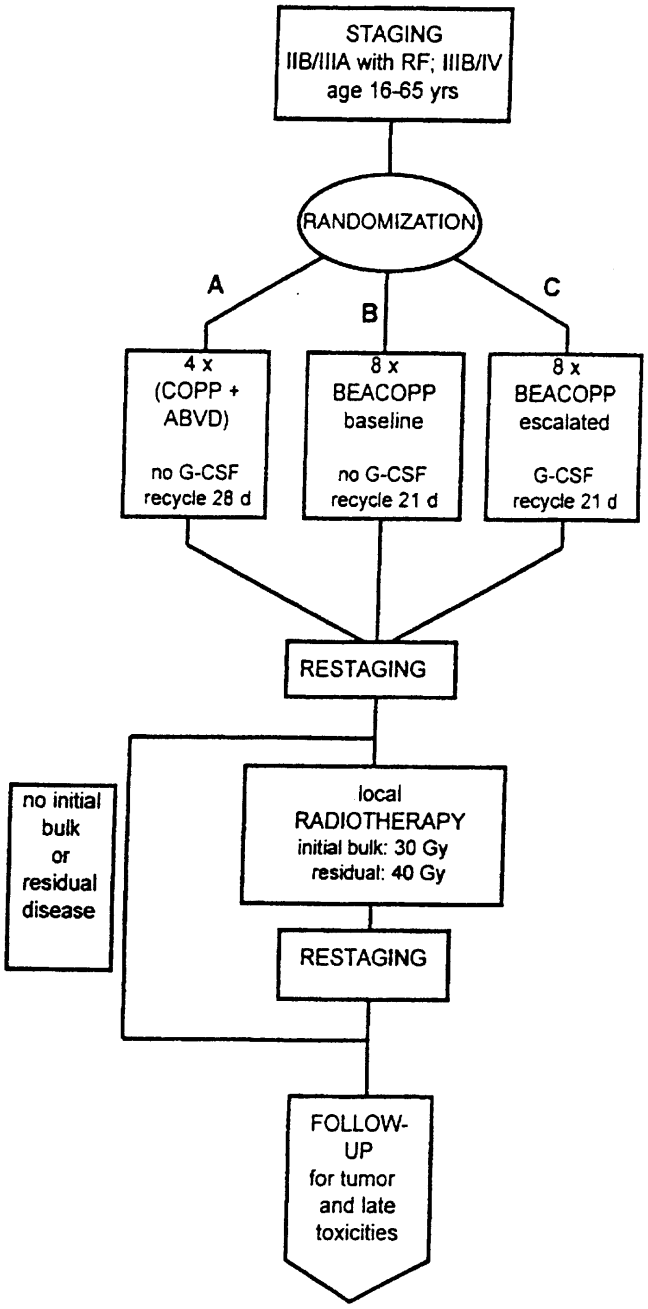

Fig 1. Flow diagram for the HD9 trial.

Trial Design

The hypothesis to be tested was that both the use of the accelerated BEACOPP regimen instead of COPP/ABVD and the moderate dose escalation of cyclophosphamide, etoposide, and doxorubicin would lead to increased efficacy and to improved long-term treatment results.

Patients were randomized into three arms as follows (Fig 1): arm A, 4 double cycles of COPP + ABVD + radiotherapy (RT); arm B, 8 cycles of BEACOPP baseline + RT; and arm C, 8 cycles of BEACOPP escalated (with G-CSF) + RT.

Randomization was stratified by center, stage, and large mediastinal involvement according to a version of the minimization method.[21] Randomization was performed by computer when the patient was entered and declared eligible and the outcome passed on immediately to the responsible clinician by telephone. Neither clinician nor patient could be blinded in this trial. Recruitment in arm C began 1 year later after completion of the dose-finding study, but was then preferentially randomized (by specifying unequal probabilities for assignment to each arm) to enable it to catch up with the other two arms.

Table 1. Planned Dosage and Schedule of COPP/ABVD and BEACOPP Regimens

	COPP/ABVD		BEACOPP Baseline		BEACOPP Escalated	
	Single Dose*	On Days	Single Dose*	On Days	Single Dose*	On Days
Bleomycin	10	29, 43	10	8	10	8
Etoposide	—	—	100	1-3	200	1-3
Doxorubicin	25	29, 43	25	1	35	1
Cyclophosphamide	650	1, 8	650	1	1,200	1
Vincristine	1.4†	1, 8	1.4†	8	1.4†	8
Procarbazine	100	1-14	100	1-7	100	1-7
Prednisone	40	1-14	40	1-14	40	1-14
Vinblastine	6	29, 43	—	—	—	—
Dacarbazine	375	29, 43	—	—	—	—
Repeat on day		57		22		22

*Doses given in milligrams per meter squared.
†Absolute dose of vincristine limited to 2.0 mg.

Schedules and dosages of the three regimens are listed in Tables 1 and 2. The planned daily dose of G-CSF in arm C was 300 or 480 μg for patients with body weight less than or greater than 75 kg, respectively, to be administered from day 8 until leukocyte recovery (3 days at greater than 1,000/μL). Postponement of the next cycle was specified in arms A and B until the leukocyte and thrombocyte values recovered to at least 2,500/μL and 80,000/μL, respectively, with a 25% dose reduction of all myelotoxic substances after a toxicity-related postponement of 2 weeks or more. In arm C, a stepwise dose reduction of cyclophosphamide and etoposide was planned, with four steps from escalated to baseline dose, in the event of severe leukopenia, thrombocytopenia, any WHO grade IV toxicity, or 2-week postponement, with immediate reduction to baseline doses if this occurred in two successive cycles.

RT was administered locally only to patients with initial bulky disease (≥ 5 cm diameter: 30 Gy) or residual tumor (40 Gy).

Table 2. Planned Total Dose and Dose-Intensity of COPP/ABVD and BEACOPP Regimens

	4 × COPP - ABVD		8 × BEACOPP Baseline		8 × BEACOPP Escalated	
	TD	DI	TD	DI	TD	DI
Bleomycin	80	2.5	80	3.3	80	3.3
Etoposide	—	—	2,400	100	4,800	200
Doxorubicin	200	6.3	200	8.3	280	11.7
Cyclophosphamide	5,200	163	5,200	217	10,000	417
Vincristine	11.2	0.35	11.2	0.46	11.2	0.46
Procarbazine	5,600	175	5,600	233	5,600	233
Prednisone	2,240	70	4,480	187	4,480	187
Vinblastine	48	1.5	—	—	—	—
Dacarbazine	3,000	94	—	—	—	—
Duration of CT, weeks	32		24		24	

NOTE. DI was calculated as total dose administered divided by duration of therapy from the first day of the first cycle to the last day of administration (of any drug) in the last given cycle.

Abbreviations: TD, total dose of chemotherapy; DI, dose-intensity in milligrams per meter squared per week; CT, chemotherapy.

Specifications for the restaging included clinical examination and imaging or biopsy methods appropriate to the sites of initial involvement (CT, radiograph, sonography, bone scintigraphy, or bone marrow or liver biopsy). Complete remission could include the presence of residues, especially in the mediastinum, when there was no sign of active tumor provided that a therapy-related origin for these residues (eg, radiation fibrosis) was plausible. The irradiated fields included neighboring lymph node chains (ie, involved field) to 30 Gy for initial bulk or residual involvement in the neighborhoods of left neck, right neck, mediastinum (clavicular chains irradiated), or paraaortal-spleen-liver hilus. RT began 2 to 4 weeks after the end of chemotherapy in daily fractions of 1.8 to 2.0 Gy.

Follow-up examinations (clinical, blood measurements, thorax radiograph, abdominal sonography) were specified at 3-month intervals in the first 2 years, 4-month intervals in the third and fourth year, and 6-month intervals thereafter. CT of the thorax and abdomen, skeletal scintigraphy, and biopsy of liver and bone marrow should be performed if relapse was suspected. For HD9 patients who relapsed, curative RT was recommended when possible. Otherwise, the salvage chemotherapy regimen dexamethasone, carmustine, etoposide, cytarabine, and melphalan (DexaBEAM) was recommended,[22] with or without high-dose chemotherapy supported by hematopoietic stem-cell transplantation.

Biometry

The trial was designed to detect differences between the three arms with FFTF as the main end point and survival as the subsidiary end point. Events for FFTF were progression, lack of CR at the end of protocol therapy, and relapse and death from any cause; therefore, in contrast to relapse-free or progression-free survival, toxic and unrelated deaths were counted. Events for survival were all deaths from whatever cause. Both survival and FFTF were measured from randomization to occurrence of the first event or last follow-up examination. To reach 80% power to detect a 9% to 10% difference in the 5-year FFTF rate, a required sample size of at least 900 patients was calculated.[23]

An intent-to-treat analysis was planned, according to randomization. Randomization outcome could be altered only if the criteria for exclusion were discovered before the initiation of therapy or if the pathology review retrospectively refuted the diagnosis of HD.

Interim analyses were planned at 2, 3, 4, and 5 years after starting recruitment into arm C. The final analysis was to be performed when circa 400 FFTF events had occurred (truncation). A full description of the sequential design and analysis strategy is given in the Appendix.

To avoid bias caused by the effect "bad news travels quickly," the inclusion criteria for patients in each interim analysis were chosen as follows. The included patients were those who had been recruited at least 18 months before the analysis was performed so that all had adequate time to complete therapy and restaging. Efforts were then made to achieve a high percentage of assessable patients within this sample by actively following up all cases with incomplete documentation. Assessable cases were defined as those with fully documented staging and either status-definitive follow-up documentation at least 3 months after the end of therapy according to protocol or fully documented early termination of therapy with disease status and reason for termination.

Survival analysis was performed according to the Kaplan-Meier method, and subgroups were compared using the log-rank test. The effect of the following prognostic factors on the arm comparison was investigated by Cox's proportional hazards regression: age, stage IVB, laparotomy, large mediastinal mass, E stage, elevated erythrocyte sedimentation rate, and low hemoglobin level (< 12.0 g/dL for men, < 10.5 g/dL for women).

RESULTS

First Interim Analysis Leading to Termination of Arm A

The first interim analysis (2 years after starting arm C recruitment) was initiated in May 1996 and completed in September 1996. The target cohort was set to include all patients randomized to treatment before November 1, 1994. There were 339 randomized patients, of whom 321 (95%) were assessable; 125 in arm A, 131 in arm B, and 65 in arm C (because recruitment began later). Patient characteristics were well balanced between arms.

Seventy-one FFTF events were observed; 41 in arm A (COPP/ABVD) and 30 in arms B and C pooled (BEACOPP). Nominal estimates of FFTF rate at 2 years were 70% for COPP/ABVD and 83% for pooled BEACOPP. The test for a difference in FFTF between arms A and B + C gave a nominal P (P_{nom}) of .0007, which fulfilled the criteria of the sequential design for significance at the 5% level. In fact, such a P would qualify for significance using any recognized sequential plan. The global test for differences in FFTF between the three arms gave a P_{nom} of .0011. The inferiority of arm A indicated by the FFTF results was confirmed by a multivariate analysis using Cox regression. Comparisons of CR rate (76% arm A, 89% arms B + C) and progression rate (16% arm A, 7% arms B + C; P_{nom} = .007) between COPP/ABVD and pooled BEACOPP indicated that, whatever may be shown in future analyses concerning long-term relapse rates, BEACOPP showed improved results immediately at the end of therapy. The comparison between baseline and escalated BEACOPP (arm B *v* arm C) lacked power because of the small number of events observed and showed no significant difference when analyzed according to the sequential plan.

Second Interim Analysis

In April 1997, the second interim analysis was performed, taking as target cohort all patients randomized before October 1, 1995. This cohort consisted of 550 patients, of whom 505 (92%) were assessable; 182 in arm A, 185 in arm B, and 138 in arm C. The median observation time was 23 months. In addition to these 550 patients, 30 other randomizations within this period had been cancelled for the following reasons: HD diagnosis refuted (n = 22); composite lymphoma (n = 1); randomized onto wrong trial (n = 4); concurrent disease (n = 2); and patient moved abroad 2 weeks after randomization (n = 1). Four patients randomized onto arm C refused escalated BEACOPP immediately after randomization: three chose COPP + ABVD and one chose BEACOPP baseline; these randomizations were also

cancelled. However, an analysis by strict intent to treat, which retained the original random allocation of these four patients, was also performed; because all these patients were in continuous complete remission, this did not appreciably affect the results.

There were 13, 15, and 17 nonassessable patients in arms A, B, and C, respectively. The higher rate of nonassessability in arm C can be explained by the late start for randomization of this group. In 30 patients, no documentation of therapy or outcome had been received, whereas for seven patients, documentation was complete except for the obligatory follow-up form. The proportions of such cases did not differ appreciably between treatment arms. Inquiries to the responsible institutions showed that 27 of the 45 patients were in continuing CR, five had progressed or relapsed (two after COPP/ABVD and three after BEACOPP), one had died (arm B), and one terminated treatment early (arm A). No information was available in 11 patients (2%).

Table 3. Patient Characteristics for Second Interim Analysis, April 1997

	Arm A, COPP/ABVD	Arm B, BEACOPP Baseline	Arm C, BEACOPP Escalated
Age, years			
< 50	85	82	85
50-60	8	13	12
> 60	7	5	3
Sex			
Men	43	38	36
Women	57	62	64
Histological subtype (reviewed)			
LP	3	3	1
NS grade 1	51	48	58
NS grade 2	12	12	11
MC	23	20	20
LD	2	5	3
Unclassified	8	5	2
HD uncertain	2	7	5
Stage			
IIB	8	15	14
IIIA	32	24	20
IIIB	31	24	31
IVA	7	11	10
IVB	21	27	25
Laparotomy	11	8	5
Karnofsky index ≤ 8	20	25	25
Hemoglobin < 12 g/dL (men) or < 10.5 g/dL (women)	25	33	24
Prognostic index			
0-1	39	32	33
2-4	58	60	62
5-7	3	8	5
Total	n = 182	n = 185	n = 138

NOTE. Values indicate percentage of patients. The histologic subtype was reviewed in 70% of the cases; these percentages refer to reviewed cases only.

Abbreviations: LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion.

Table 4. Treatment Results for Second Interim Analysis, April 1997

	Arm A COPP/ABVD		Arms B + C BEACOPP	
	No.	%	No.	%
CR	151	83	298	92
PR	2	1	3	1
Progress	22	12	18	6
Unknown*	7	4	4	4
CR, unknowns excluded		86		93
Relapse	15		18	
Death†	20		17	
Total no. of events	49		46	
Total no. of patients	182		323	

*Unknown indicates no restaging result was documented at the termination of therapy, usually because of death during therapy from non-HD causes. These cases have been excluded in calculating the CR rate.

†Not mutually exclusive to other events.

Patient characteristics are compared between arms in Table 3. There are no marked imbalances. Arm A has somewhat fewer stage IV patients but slightly more patients aged older than 60 years (although fewer aged 50 to 60 years) and more mixed cellularity cases. The liver was involved in 12% of all patients; diffuse organ involvement was recorded mainly in the bone marrow (8%), lung (7%), bone (4%), and pleura (4%). The prognostic index was calculated as recommended by Hasenclever et al[24] based on the analysis of the International Prognostic Factors Project for advanced HD.

Ninety-five FFTF events were observed, 49 in arm A and 46 in arms B + C pooled. Treatment results confirmed the findings of the first interim analysis (Table 4). In the analysis

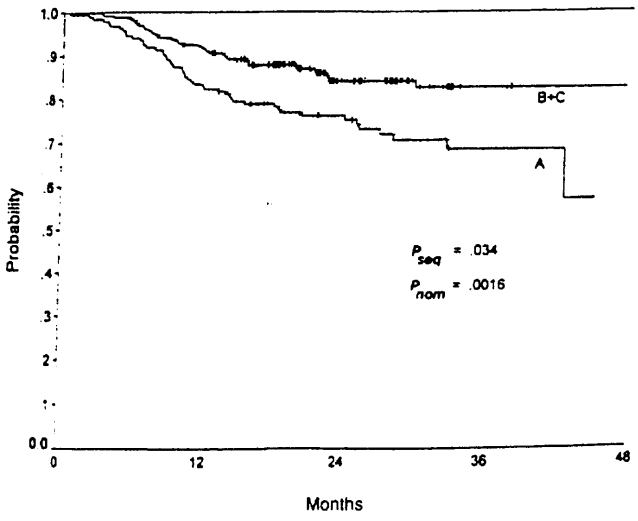

Fig 2. FFTF for arm A (COPP/ABVD) versus pooled arms B and C (BEACOPP); second interim analysis, April 1997. Curves are labeled with number of events/number of patients. Significance levels P_{nom} and P_{seq}.

of the main end point, FFTF, which allowed for sequential monitoring, results for pooled BEACOPP were significantly better than for COPP/ABVD (P_{nom} = .0016; P according to sequential analysis [P_{seq}] = .034; Fig 2). The median unbiased estimate of the hazards ratio was 0.64 (adjusted 95% confidence interval, 0.42 to 0.97). This corresponds to a relative risk of approximately 0.66 (95% confidence interval, 0.46 to 0.96). Median unbiased estimates of FFTF rates at 2 years were: COPP/ABVD 75% and BEACOPP 84%. Sufficient information to compare escalated and baseline BEACOPP (arms C and B) with respect to FFTF or survival had not been accumulated at this interim analysis. Therefore, no further information on the comparison of treatment results for arms B and C will be disclosed at this stage.

Multivariate analysis of FFTF by Cox regression found the significant factors to be arm (A v B + C pooled, P_{nom} = .0013) and stage. Survival is of only borderline nominal significance (Fig 3; P_{nom} = .039); this cannot be regarded to have overall significance with respect to the sequential plan. The CR rates (92% v 83%; P_{nom} = .0014) and progression rates (6% v 12%; P_{nom} = .0092) are both better with BEACOPP (pooled) than with COPP/ABVD.

Causes of death are shown in Table 5. The most common was HD (13 deaths), followed by acute toxicity during primary chemotherapy (seven deaths) and acute toxicity during salvage therapy (six deaths). In two patients, the cause of death was not available. There were more toxic deaths during COPP/ABVD chemotherapy than during BEACOPP (five v two deaths). All toxic deaths in primary chemotherapy were caused by sepsis (four deaths), pneumonia (two deaths), or both (one death).

Acute toxicity (Tables 6 and 7) under baseline BEACOPP

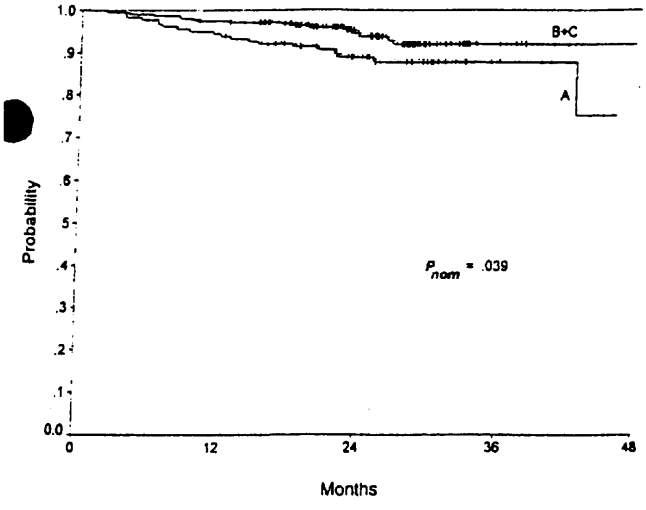

Fig 3. Survival for arm A (COPP/ABVD) versus pooled arms B and C (BEACOPP); second interim analysis, April 1997. Curves are labeled with number of events/number of patients.

Table 5. Causes of Death for Second Interim Analysis, April 1997

	Arm A: COPP/ABVD	Arms B + C, BEACOPP
Hodgkin's disease	6	7
Acute toxicity, salvage	3	3
Acute toxicity, primary	5	3*
Leukemia	–	1
NHL	2	1
Cardiac	1	–
Other/unknown	3	2
Total deaths/patients	20/182	17/323

NOTE. Values indicate number of patients who died from the given cause.
*One during RT.

was similar in severity to that experienced under ABVD. With escalated BEACOPP, the documented hematologic toxicities were more severe, but this resulted in infections of WHO grade 3 or 4 in only 3% of all cycles, similar to baseline BEACOPP. BEACOPP chemotherapy was administered on schedule and close to the planned dose in both escalated and baseline versions for the majority of patients (Tables 8 and 9). The drugs escalated in arm C had a somewhat larger dose reduction, on average, than the same drugs in arms A and B, but despite this, the absolute doses were still substantially larger. More patients received local adjuvant RT in arms B and C (each 66%) than in arm A (58%; Table 10). This discrepancy is at least partly because of the greater frequency of initial bulky disease in arms B and C patients (59%, 69%, and 71% in arms A, B, and C, respectively).

Among the 15 patients who relapsed after COPP/ABVD, two received at most palliative therapy, three received RT, four received escalated-dose DexaBEAM chemotherapy, four received high-dose chemotherapy with stem-cell transplantation, and two are unknown. Of the 18 patients who relapsed after BEACOPP, three received at most palliative therapy, one received escalated-dose DexaBEAM chemother-

Table 6. Acute Hematologic Toxicity for Second Interim Analysis, April 1997

	WHO Grade	COPP	ABVD	BEACOPP Baseline	BEACOPP Escalated
Leukopenia	1-2	33	39	38	17
	3-4	8	41	36	78
Thrombocytopenia	1-2	4	8	6	29
	3-4	1	1	2	36
Anemia	1-2	19	21	51	63
	3-4	–	1	6	27
Infection	1-2	5	8	9	16
	3-4	–	1	3	3
No. of documented cycles		615	615	1,140	854

NOTE. Values indicate percentages of documented cycles in which a toxicity of the given kind and WHO grade was recorded. Grades 3 to 4 toxicities are defined as follows[38]: leukopenia < 2,000/μL, thrombocytopenia < 50,000/μL, anemia < 8 g/mL; serious infection.

Table 7. Other Acute Toxicities for Second Interim Analysis, April 1997

	WHO Grade	COPP	ABVD	BEACOPP Baseline	BEACOPP Escalated
Hair loss	1-2	32	35	21	19
	3-4	19	20	52	64
Nausea	1-2	32	34	36	40
	3-4	5	10	5	5
Neurologic	1-2	21	16	28	29
	3-4	2	2	1	< 1
Mucositis	1-2	3	4	9	21
	3-4	< 1	< 1	< 1	1
Pain	1-2	3	3	10	15
	3-4	< 1	< 1	< 1	2
Digestive system	1-2	5	5	7	10
	3-4	< 1	< 1	< 1	< 1
Respiratory	1-2	2	3	7	8
	3-4	< 1	< 1	< 1	< 1
Skin	1-2	2	2	7	8
	3-4	< 1	< 1	< 1	< 1
Medication fever	1-2	2	5	4	7
	3-4	—	1	< 1	< 1
Cardiac	1-2	—	< 1	3	3
	3-4	—	< 1	< 1	< 1
Allergy	1-2	1	1	4	1
	3-4	—	—	< 1	< 1
No. of documented cycles		615	615	1,140	854

NOTE. Values indicate percentages of documented cycles in which a toxicity of the given kind and WHO grade was recorded.[38]

apy, 10 received high-dose chemotherapy with stem-cell transplantation, and four are unknown. One of 15 COPP/ABVD patients who relapsed and four of 18 BEACOPP patients who relapsed died (log-rank $P = .16$ from a Kaplan-Meier analysis of survival after relapse).

G-CSF was administered in 4% of the COPP courses, 14% of the ABVD courses, 10% of the baseline BEACOPP courses, and 90% of the escalated BEACOPP courses. On average, G-CSF was administered over a period of 4.9 days per course in arm C.

Of the 323 BEACOPP patients, six have had a second malignancy (one myelodysplastic syndrome (MDS), two acute myeloid leukemias (AMLs), two non-Hodgkin's lymphomas (NHLs), one melanoma), of which the MDS and one NHL were fatal. Both AMLs had a t(9;11) translocation. Five of 182 COPP/ABVD patients have had a second malignancy, all NHLs, of which three were fatal (the review pathology panel confirmed four of these five cases as primary HD, whereas in one case the diagnosis was uncertain on technical grounds).

Table 8. Duration of Chemotherapy for Second Interim Analysis, April 1997

	4 COPP/ ABVD, %	8 BEACOPP Baseline, %	8 BEACOPP Escalated, %
Duration, weeks			
22-24	—	58	56
25-27	—	29	28
28-31	35	12	13
32-35	35	1	2
36-39	22	—	1
40-	7	1	—
Median duration, weeks	33.4	24.6	24.7
Planned duration, weeks	30	23	23

NOTE. Values indicate percentage of all patients with documented first and final (fourth double or eighth) cycle. Duration was measured from the start of first cycle to last administration of drugs in last cycle.

Table 9. Total Administered Dose for Each Drug as a Percentage of Intended Dose for Second Interim Analysis, April 1997

	Arm A, COPP/ ABVD	Arm B, BEACOPP Baseline	Arm C, BEACOPP Escalated
Bleomycin	87	88	89
Etoposide (200)*	—	96	85 (170)†
Doxorubicin (140)*	91	95	91 (127)†
Cyclophosphamide (190)*	93	96	87 (165)†
Vincristine	86	87	82
Procarbazine	92	92	93
Prednisone	96	96	96
Vinblastine	86	—	—
Dacarbazine	90	—	—

NOTE. Mean over all patients for whom all administered cycles were documented.

Dose escalation (%) compared with arm B planned dose in parentheses: * planned; and † administered.

DISCUSSION

In light of these findings, it appears very unlikely that the classic COPP/ABVD scheme is as efficacious as the best variant (or both) of BEACOPP with respect to disease control for advanced-stage patients as a whole. Conversely, no conclusive comparison between the two BEACOPP variants, baseline and escalated dose, was possible because of insufficient information. It was therefore decided after the first interim analysis to stop recruitment onto arm A (COPP/ABVD) and to continue with arms B and C as a two-armed study, on the following grounds.

First, the formal criterion in the sequential plan was satisfied: significant inferiority of arm A in FFTF compared with pooled BEACOPP results. Second, an adequate number

Table 10. Administration of Radiotherapy for Second Interim Analysis, April 1997

	Arm A	Arm B	Arm C
Initial bulky disease, %	59	69	71
Residual tumor, %*	34	43	39
Radiation indicated	69	78	79
Radiation documented	58	66	66
No.	182	185	138

*Information on restaging results after end of chemotherapy was available for 94% of patients.

of patients (257 patients; planned size, 300 patients) had already been randomized to arm A to allow a comparison with sufficient statistical power with each BEACOPP arm in the final analysis. In addition, the arm A results in HD9 were similar to results with similar patients in our previous trial, HD6, in which essentially the same treatment was administered to 300 patients. This indicates that patient accrual to HD9 had similar characteristics compared with previous advanced-stage trials of the GHSG. Third, the acute toxicity of BEACOPP was shown to be acceptable and manageable in the multicenter setting. Fourth, the BEACOPP pilot and dose-finding studies had already shown promising results with a somewhat longer follow-up. The planned sample size was increased to 500 in each of arms B and C to permit a more exact comparison of both survival (SV) and FFTF between the two BEACOPP variants.

The BEACOPP regimens have thus been shown to give equal or (more likely) superior FFTF compared with our standard regimen. This is consistent with the results from the pilot and dose-finding studies, in each of which FFTF rates of 90% at 24 months were obtained.[17,18] The lower progression rate makes a substantial contribution to this improvement in treatment success. However, it is not yet clear whether results with escalated BEACOPP are different from those with baseline BEACOPP, nor whether baseline BEACOPP is better than COPP/ABVD. In other words, we cannot conclusively assign the improvement in results either to the BEACOPP regimen per se with its inherent dose intensification because of the shorter cycle or to the dose escalation of cyclophosphamide, etoposide, and doxorubicin. Because the FFTF values at 24 months differ by 9% between COPP/ABVD and BEACOPP pooled, we can expect that, with increasing sample size and longer observation times, the relative positions of the three arms with respect to FFTF will become clear over the next few years. It is not yet clear whether the results agree in detail with the model described in the introduction, but the observed improvement in FFTF for pooled BEACOPP agrees with the 9% predicted by the model (a weighted average of the predictions for arms B and C).

The survival benefit of BEACOPP is not yet proven. Although survival is perhaps ultimately the most important measure of treatment suitability, FFTF was chosen as the main end point in this trial for two reasons: first, a continuing complete remission is valuable in itself and, second, survival events occur more rarely and later; thus, an analysis by FFTF is more sensitive and can reach a conclusion earlier. The improved FFTF and the lack of an increased rate of acute toxic deaths leads us to expect a moderate improvement in survival, but as yet we cannot assess the prognosis under salvage therapy for patients who were primarily treated with BEACOPP. With only five deaths after relapse reported thus far, it is too early to compare survival after relapse after these two regimens. Late toxicities after BEACOPP are also still unknown. Because survival after COPP/ABVD therapy has not been shown to be inferior to that after BEACOPP, we recommended that patients who already began with COPP/ABVD continue to receive this regimen as scheduled.

We report here an early interim analysis in which just 95 events have been observed; originally, the final analysis was planned to take place after 400 events. All results should therefore be treated with caution because (1) precision is still low because of the small number of events, (2) only short- to middle-term results are available (median observation time, 23 months from randomization), and (3) the treatment comparisons could be biased. The possible sources of bias are as follows.

Recruitment into arm C began later than for arms A and B. There could have been changes in the admission process over time that resulted in differences in patient characteristics in arm C compared with the other two arms. However, the documented characteristics did not differ appreciably between arms (Table 3). There was no shift in the distribution of the prognostic index before and after the opening of arm C (February 1994); other factors showed only negligible shifts, with the exception of age. The proportion of patients aged older than 50 years decreased from 23% to 11% after February 1994. Despite this shift in age, there were no consistent differences in the age distribution between COPP/ABVD and BEACOPP patients (15% and 16% were aged older than 50 years, respectively). However, other undocumented factors could differ. There could also have been a learning effect that would tend to improve the results in patients recruited later to the advantage of arm C. Yet survival analysis of arm A and B patients divided into five groups according to the date of randomization (6-month periods) showed no consistent trend in FFTF or SV with randomization period. In a comparison of FFTF between COPP/ABVD and BEACOPP (pooled) that excluded all patients randomized before the opening of arm C, the estimated superiority of BEACOPP (nominally 84% *v* 77% after 24 months; P_{nom} = .061) was somewhat reduced compared with nominal 85% versus 74% in the full analysis. The power of this restricted analysis is low because of the reduced patient numbers (97 *v* 236 patients) and number of events (20 *v* 29 events).

Another possible bias source is the difference in the lengths of COPP/ABVD and BEACOPP chemotherapy, 30 and 23 weeks, respectively. The shorter BEACOPP therapy allows less time for tumor shrinkage before restaging after chemotherapy, which would mean a higher rate of residual

tumor at this point in time and consequently more patients eligible for adjuvant irradiation. Indeed, a higher partial response (PR) rate and more frequent irradiation were observed in arms B and C (Table 9). The incidence of initial bulky disease was also greater in these arms, which partially justifies the more frequent RT. A local analysis of the pattern of residual disease shows that, among all patients with documented restaging after complete chemotherapy, residual disease was found on sites that were initially not bulky in 21 of 136 COPP/ABVD patients (15%) and 52 of 265 BEACOPP patients (20%). This difference is not significant (P = .30). Because the effect concerns only approximately 5% of the patients (who might have received irradiation after BEACOPP that they would not have received after COPP/ABVD), the effect on the overall FFTF rate is unlikely to be more than ±1%. Moreover, the role of RT as a consolidation after adequate chemotherapy for the advanced stages has been assessed by meta-analysis as very limited.[25] A benefit of 11% in FFTF at 10 years (none in survival) because of additional RT was estimated, but only six chemotherapy cycles were administered in most trials included. With eight cycles, as in our protocol, and a much shorter follow-up (2½ years), smaller benefits would be expected, and the possible contribution to the observed FFTF difference between arms would again be inferred to be of the order of 1% or less.

Finally, bias might have been contributed by differences in frequency and/or quality of follow-up because of either the late opening of arm C or the shorter duration of BEACOPP therapy (these two effects would tend to act in opposite directions). In fact, the number of follow-up sheets received did not differ greatly between arms; the average was 3.5, 3.7, and 3.2 for arms A, B, and C, respectively (counting only patients who did not die or terminate before follow-up), at intervals of 5.9, 5.6, and 5.1 months on average.

Reports from randomized trials suggest that ABVD alone is equally effective to MOPP/ABVD and to hybrid MOPP/ABVD.[4,26] Because of its moderate toxicity with respect to fertility and secondary leukemia,[26,27] ABVD is widely regarded as a standard treatment. However, the cardiac and pulmonary toxicities of ABVD could be considerable.[28] We have as yet insufficient data on fertility after BEACOPP, but it is to be expected that, as with COPP/ABVD, a high proportion of male patients will be sterile.[29] However, if disease control with BEACOPP proves to be considerably better than with ABVD, then BEACOPP would be of considerable interest at least for those patients who are less concerned about fertility. Recently, promising single-center treatment results have been obtained in advanced-stage HD that used a novel, short, and intensive chemotherapy together with irradiation.[30] This regimen has a different rationale than that previously reported, and a long-term comparison may be interesting.

High rates of secondary leukemia have been reported after chemotherapy (especially MOPP, alkylating agents, and etoposide) by several investigators.[31-33] In view of a suspected concentration of MDS/leukemia cases after BEACOPP, we searched for such cases among patients previously treated with BEACOPP or COPP/ABVD (whether subsequently administered further HD treatment or not). Six cases were found among the 296 patients in the arm that received eight cycles of COPP/ABVD with local RT in the previous trial for advanced stages (recruitment from 1988 to 1992), no cases among the 31 patients in the BEACOPP pilot study (recruitment in 1992), and two cases among 60 patients in the BEACOPP dose-finding study (recruitment from 1992 to 1993). A Kaplan-Meier analysis of time to second leukemia based on all these trials together with HD9 (Fig 4) found no significant difference between COPP/ABVD and BEACOPP, although the results tend to suggest a greater second leukemia risk with BEACOPP (P = .11). However, with the small number of observed cases and the short observation times after BEACOPP, it is still too early to judge whether BEACOPP is especially leukemogenic; this will be carefully monitored. The t(9;11) translocation observed in both our AML cases has been seen by others in several supposedly etoposide-induced secondary leukemia cases.[34,35] Any relatively small leukemia risk must be weighed against the promise of substantially improved efficacy against HD.

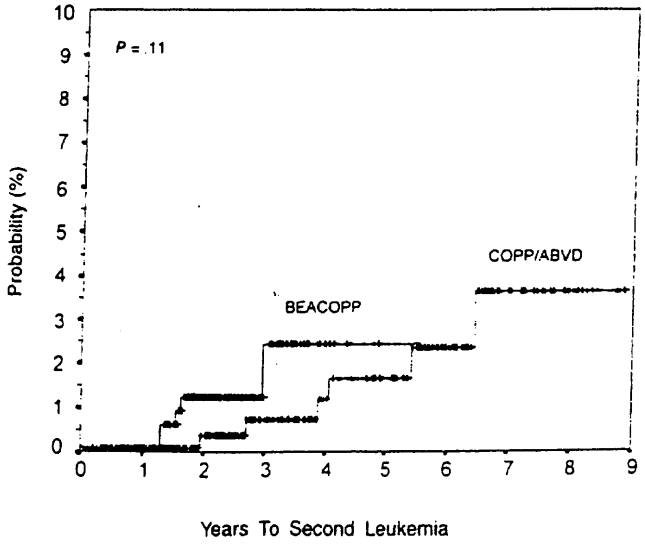

Fig 4. Kaplan-Meier plot of secondary leukemia incidence. BEACOPP (pilot study, n = 31; dose-finding study, n = 60; HD9 arms B and C, n = 323) versus COPP/ABVD (preceding advanced-stage trial HD6, COPP/ABVD arm, n = 296; HD9 arm A, n = 182). All cases were included, even if salvage therapy had been administered.

The observed secondary NHL rate was greater after COPP/ABVD (2.7%) than after BEACOPP (0.6%; $P = .050$). Because these are early cases, they may be transformations of the original malignancy rather than treatment induced. This hypothesis is consistent with the interpretation that BEACOPP is more efficacious not only against Hodgkin's tumor but also against the transformed malignant cells that lead to NHL.

Use of G-CSF was mandatory in arm C. The escalated dose levels of cyclophosphamide and etoposide were titrated under conditions of G-CSF use. It is, however, conceivable that the schedule or dosage of G-CSF could be modified, perhaps reducing costs. Work is in progress to explore this possibility.

In summary, the data presented in this interim report suggest that a new, more effective chemotherapy regimen and/or dose composition has been found for the treatment of Hodgkin's lymphoma, which could become a standard therapy. It is not yet clear whether the survival rate is increased, and more information on late toxicities is needed. We believe that our results are especially valuable because they are based on a randomized controlled comparison in a multicenter setting. Further observation and investigation of infertility, secondary leukemia, and other late toxicities after BEACOPP are required. Intriguingly, the new regimen contains only known cytotoxic and cytostatic agents in a new arrangement. If these findings are confirmed in the long run, they suggest a promising avenue for moderate dose escalation for this and possibly other malignant, chemosensitive diseases.

APPENDIX I

Sequential Design and Interim Analysis: To allow regular monitoring of the results per arm and the possibility of early termination should strong differences emerge, a truncated sequential probability ratio design was specified.[36] Using this method, at each interim analysis the log-rank statistic for an estimated arm difference in FFTF is plotted against the number of observed events, and early termination occurs when a predefined boundary is crossed. This design ensures an overall power of 80% to detect a hazards ratio of 0.7 between two arms while a type I error probability of .1 (equivalent to a one-sided error probability of .05) is maintained when interim analyses with specified termination criteria are performed. Based on results and recruitment rates from previous trials, we expected to observe approximately 50, 100, 200, and 300 events after 2, 3, 4, and 5 years of recruitment, respectively, and to reach 400 events (80% of expected events) after 7½ years.

Should one arm emerge as inferior in an interim analysis, we wanted to reserve the possibility to continue the study with the remaining two arms. The standard sequential designs are not equipped to deal with such problems of multiarm trials. However, in the case of HD9, it is natural and helpful to split the three-arm structure of the trial into two components: (1) the contrast between COPP/ABVD (arm A) and BEACOPP (arms B and C), and (2) the contrast between baseline (arm B) and escalated (arm C) BEACOPP. These comparisons are orthogonal in the statistical sense that each can be estimated independently of the other.[36] At each interim analysis, each contrast can be tested and the relevant early termination can be made when required. A discrepancy exists between choice of sample size, which was calculated to detect with 80% power a hazards ratio of 0.7 between two arms, and the analysis by orthogonal comparisons that used the pooled BEACOPP arms. The sample size in the pooled group is larger, which gives a larger power to the comparison; thus, the trial is likely to stop with a somewhat less pronounced hazards ratio than intended. A power of 80% is valid for a hazards ratio A:(B + C) of approximately 0.75. This increased sensitivity is a slight advantage although, in assessing the interim result, it should be considered that comparisons between any two arms are not necessarily significant in the sequential analysis.

Treatment results disclosed at an interim analysis because of early termination (as in the present report) are potentially misleading because of the sequential nature of the monitoring plan. First, the P_{nom} exaggerate the true significance of the results because they ignore the multiple testing at successive analyses. Second, the estimates of treatment effects (eg, the difference in FFTF values between treatments) are biased and tend to be larger than the true effects.[36,37] For the main end point (FFTF), the correct P_{seq}, unbiased estimates, and confidence intervals can be calculated. These are given first in the results section. For the secondary end points (survival, CR rate, and progression rate), correct sequential values are not available. Therefore, for reasons of consistency, the nominal values for all end points follow the sequential values for FFTF in the results section.

APPENDIX II

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