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ORIGINAL REPORT

Intensified Chemotherapy and Dose-Reduced Involved-Field Radiotherapy in Patients With Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD11 Trial

Hans Theodor Eich, Volker Diehl, Helen Görgen, Thomas Pabst, Jana Markova, Jürgen Debus, Anthony Ho, Bernd Dörken, Andreas Rank, Anca-Ligia Grosu, Thomas Wiegel, Johann Hinrich Karstens, Richard Greil, Normann Willich, Heinz Schmidberger, Hartmut Döhner, Peter Borchmann, Hans-Konrad Müller-Hermelink, Rolf-Peter Müller, and Andreas Engert

See accompaning articles on pages 4184, 4191, and 4207

From the University of Cologne; German Hodgkin Study Group, Köln; University of Heidelberg, Heidelberg; Charité-Universitätsmedizin Berlin, Berlin; University of Munich, Munich; University of Freiburg, Freiburg; University of Ulm, Ulm; University of Hannover, Hannover; University of Muenster, Muenster; University Hospital Mainz, Mainz; University of Würzburg, Würzburg, Germany; Swiss Group for Clinical Cancer Research, Bern, Switzerland; University Hospital Kralovske Vinohrady, Charles University, Prague, Czech Republic; and University Salzburg, Salzburg, Austria.

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Corresponding author: Andreas Engert, MD, University of Cologne, Department of Internal Medicine I, Kerpener Str. 62, 50924 Cologne, Germany; e-mail: a.engert@uni-koeln.de.

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ABSTRACT

Purpose
Combined-modality treatment consisting of four to six cycles of chemotherapy followed by involved-field radiotherapy (IFRT) is the standard of care for patients with early unfavorable Hodgkin's lymphoma (HL). It is unclear whether treatment results can be improved with more intensive chemotherapy and which radiation dose needs to be applied.

Patients and Methods
Patients age 16 to 75 years with newly diagnosed early unfavorable HL were randomly assigned in a 2 × 2 factorial design to one of the following treatment arms: four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) + 30 Gy of IFRT; four cycles of ABVD + 20 Gy of IFRT; four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{baseline}$) + 30 Gy of IFRT; or four cycles of $BEACOPP_{baseline}$ + 20 Gy of IFRT.

Results
With a total of 1,395 patients included, the freedom from treatment failure (FFTF) at 5 years was 85.0%, overall survival was 94.5%, and progression-free survival was 86.0%. $BEACOPP_{baseline}$ was more effective than ABVD when followed by 20 Gy of IFRT (5-year FFTF difference, 5.7%; 95% CI, 0.1% to 11.3%). However, there was no difference between $BEACOPP_{baseline}$ and ABVD when followed by 30 Gy of IFRT (5-year FFTF difference, 1.6%; 95% CI, −3.6% to 6.9%). Similar results were observed for the radiotherapy question; after four cycles of $BEACOPP_{baseline}$, 20 Gy was not inferior to 30 Gy (5-year FFTF difference, −0.8%; 95% CI, −5.8% to 4.2%), whereas inferiority of 20 Gy cannot be excluded after four cycles of ABVD (5-year FFTF difference, −4.7%; 95% CI, −10.3% to 0.8%). Treatment-related toxicity occurred more often in the arms with more intensive therapy.

Conclusion
Moderate dose escalation using $BEACOPP_{baseline}$ did not significantly improve outcome in early unfavorable HL. Four cycles of ABVD should be followed by 30 Gy of IFRT.

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INTRODUCTION

Patients with Hodgkin's lymphoma (HL) in early unfavorable stages are usually being treated with a combination of chemotherapy and involved-field radiotherapy (IFRT). This combined-modality treatment consisting of four to six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by IFRT at doses of 30 to 36 Gy has resulted in up to 80% long-term tumor control.[1-3] However, when compared with early favorable disease, the outcome in early unfavorable HL leaves room for further improvement.[4,5] Thus, the primary goal of current treatment approaches in this group is to improve tumor control.

To optimize the treatment for patients with early unfavorable HL, the German Hodgkin Study Group (GHSG) conducted the randomized HD11 multicenter trial presented here in which the standard of care regimen, ABVD, was compared with the more intensive bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine,

and prednisone ($BEACOPP_{baseline}$) regimen. The second major goal of this trial was to determine the best radiation dose needed in this combined-modality approach. Thus, chemotherapy was followed by IFRT given in either a 30- or 20-Gy dose.

PATIENTS AND METHODS

Patients

Entry onto the trial was restricted to patients with histology-proven HL of any histologic subtype in clinical stages IA, IB, or IIA with at least one of the following risk factors: bulky mediastinal mass (≥ one-third maximum transverse thorax diameter); extranodal involvement; erythrocyte sedimentation rate (ESR) ≥ 50 mm/h or ≥ 30 mm/h in patients with "B" symptoms; or three or more lymph node areas involved. In addition, patients with stage IIB disease and ESR ≥ 50 mm/h or ≥ 30 mm/h and B symptoms or three or more involved lymph node areas, but neither of the two other risk factors (bulky mediastinal mass, extranodal involvement), were also included.

Patients had to be between 16 and 75 years old, previously untreated, free of concurrent disease, and have a WHO activity index of less than 3. Patients with impaired heart, lung, liver, or kidney function; previous malignant disease; or HIV-positive status were not included. Patients were also excluded from the study if they had chronic obstructive lung disease, were pregnant or lactating, or had HL as part of a composite lymphoma. Minimal hematologic requirements were a WBC count of more than 3,000/μL and platelet count of more than 100,000/μL. After initial diagnosis by the local pathologist, biopsy material was centrally reviewed by at least one member of a panel of six HL pathology experts. All patients gave written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonization and national regulations. The protocol was reviewed and approved by the ethics committee at each participating institution. The study was conducted in accordance with the Declaration of Helsinki and registered as NCT00264953 (ClinicalTrials.gov).

Study Design

A 2 × 2 factorial design was chosen to potentially demonstrate superiority of the $BEACOPP_{baseline}$ regimen over ABVD and to test noninferiority of 20 Gy compared with 30 Gy of IFRT. Patients were randomly assigned at equal ratios to one of the following four arms: arm A, four cycles of ABVD followed by 30 Gy of IFRT; arm B, four cycles of ABVD followed by 20 Gy of IFRT; arm C, four cycles of $BEACOPP_{baseline}$ followed by 30 Gy of IFRT; and arm D, four cycles of $BEACOPP_{baseline}$ followed by 20 Gy of IFRT. Random assignment was performed centrally by telephone according to the minimization method.[6] Stratification factors included center, age ($< v \geq 50$ years), supradiaphragmatic or infradiaphragmatic involvement, B symptoms, and extranodal involvement.

The primary efficacy end point was freedom from treatment failure (FFTF); secondary end points included overall survival (OS), progression-free survival (PFS), response rates, and toxicity of treatment. FFTF was defined as the time from completion of all staging examinations to the first of the following events: progression or relapse, salvage therapy after no change or partial response as final treatment outcome, death from any cause, or treatment discontinuation for reasons other than concurrent disease when the final treatment outcome was unknown. FFTF was censored in patients with treatment discontinuation in whom further treatment was unknown or significantly more intensive than the study treatment and at the date of last information on the tumor status. OS and PFS were calculated from the same starting date as FFTF. OS was censored at the date of last information. PFS was defined as survival until progression, relapse, or death from any cause and was censored at the date of last information on tumor status. Definitions of complete remission, partial remission, no change, progressive disease, and relapse have been previously described.[3]

Hypotheses

To test the difference between the two chemotherapy regimens, the Kaplan-Meier curve for FFTF of pooled arms A and B was to be compared with the respective Kaplan-Meier curve of pooled arms C and D by a stratified log-rank test with significance level of $\alpha = .05$. For testing noninferiority of 20 Gy compared with 30 Gy of IFRT, the 5-year FFTF rate of pooled arms A and C was to be compared with the 5-year FFTF rate of pooled arms B and D; if the

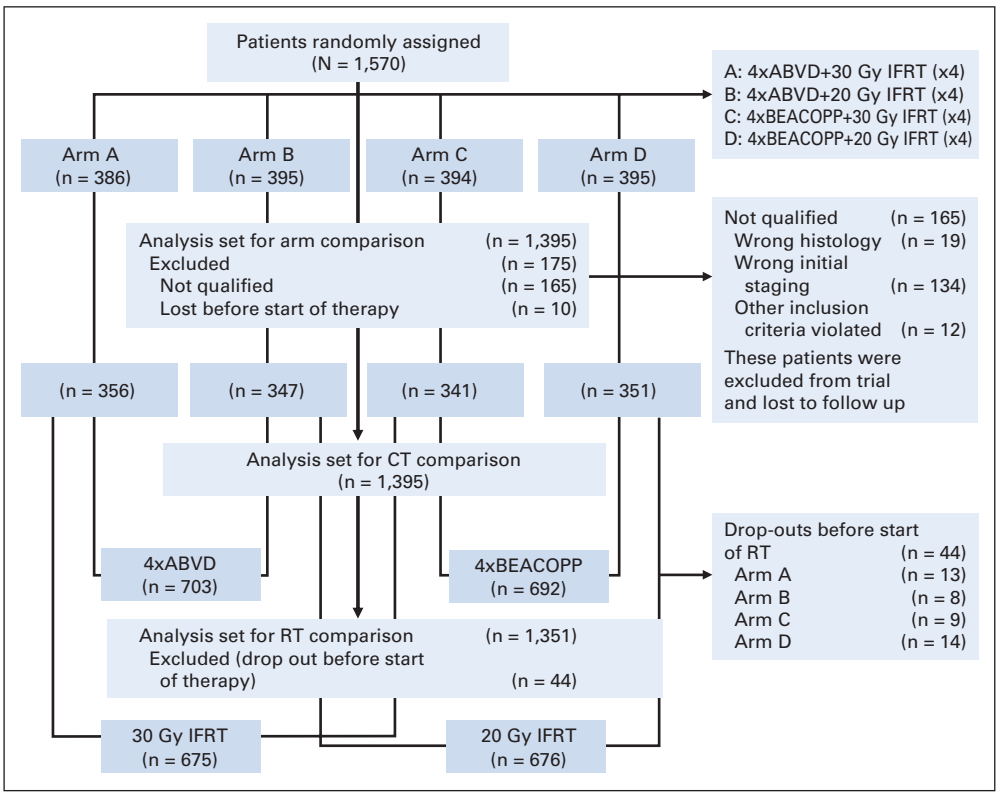

Fig 1. Patient flow of the HD11 study. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IFRT, involved-field radiotherapy; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CT, chemotherapy; RT, radiotherapy.

lower bound of the 95% CI for the difference exceeded the noninferiority bound of −7% (as defined in the study protocol), 20 Gy of IFRT would be noninferior to 30 Gy of IFRT. Interaction between the effects of chemotherapy and radiotherapy had to be excluded to justify pooling of treatment arms.

As stated in the protocol, a minimal sample size of at least 900 patients was necessary to achieve a power of 80% for the analysis of the main effects (chemotherapy and radiotherapy comparison with pooled arms). However, in case of interaction between chemotherapy and radiotherapy effects, considerably more patients would be necessary to obtain equal power.

Chemotherapy

ABVD was administered at standard doses consisting of doxorubicin 25 mg/m^2 (days 1 and 15), bleomycin 10 mg/m^2 (days 1 and 15), vinblastine 6 mg/m^2 (days 1 and 15), and dacarbazine 375 mg/m^2 (days 1 and 15) with repetition on day 29. BEACOPP$_{baseline}$ included cyclophosphamide 650 mg/m^2 (day 1), doxorubicin 25 mg/m^2 (day 1), etoposide 100 mg/m^2 (days 1 through 3), procarbazine 100 mg/m^2 (days 1 through 7), prednisone 40 mg/m^2 (days 1 through 14), vincristine 1.4 mg/m^2 (day 8), and bleomycin 10 mg/m^2 (day 8), repeated on day 22.[5] In both arms, treatment was postponed until recovery of WBC count to more than 2,500/μL or the platelet count to more than 80,000/μL on the day scheduled for re-treatment. Granulocyte colony-stimulating factor (G-CSF) was not mandatory for either regimen and given according to American Society of Clinical Oncology guidelines.

Radiotherapy

All patients received either 30 or 20 Gy of IFRT in single fractions of 1.8 to 2.0 Gy administered five times weekly. The definition of IFRT is given elsewhere.[3] To optimize the quality of radiotherapy, a comprehensive quality control program was conducted based on central review of diagnostic imaging. An individual radiotherapy plan was provided for each patient, and the expert radiotherapy panel retrospectively evaluated the following items: radiation fields, radiation doses applied, treatment duration, and technical parameters according to the initial radiotherapy plan.[7]

RESULTS

Patients

Between May 1998 and January 2003, 342 participating centers in Germany, Switzerland, Austria, Czech Republic, and the Netherlands recruited a total of 1,570 patients. One hundred sixty-five patients were not qualified as a result of wrong initial staging (n = 134), reference histology not confirming HL (n = 19), and other inclusion criteria violations (n = 12). Ten patients were excluded from all analyses because they dropped out before any treatment was given (Fig 1). Therefore, the analysis set for the chemotherapy comparison comprised 1,395 patients (356 patients in arm A, 347 in arm B, 341 in arm C, and 351 in arm D). Forty-four patients dropped out before radiotherapy and were excluded from the radiotherapy comparison, leaving 675 patients treated with 30 Gy of IFRT and 676 patients treated with 20 Gy of IFRT in the respective intent-to-treat analysis set.

Table 1. Baseline Demographics and Clinical Characteristics

	Treatment Arm*								CT Comparison*				RT Comparison†			
	4×ABVD + 30 Gy (n = 356)		4×ABVD + 20 Gy (n = 347)		4×BEACOPP + 30 Gy (n = 341)		4×BEACOPP + 20 Gy (n = 351)		4×ABVD + RT (n = 703)		4×BEACOPP + RT (n = 692)		CT + 30 Gy (n = 675)		CT + 20 Gy (n = 676)	
Demographic or Clinical Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years																
Mean	35.2		34.9		35.8		35.7		35.0		35.7		35.3		35.0	
Standard deviation	13.5		13.5		13.4		13.6		13.5		13.5		13.3		13.3	
Female	182	51	188	54	173	51	168	48	370	53	341	49	346	51	348	52
Ann Arbor stage																
IA	15	4	9	3	12	4	11	3	24	3	23	3	27	4	18	3
IB	8	2	9	3	13	4	8	2	17	2	21	3	20	3	16	2
IIA	240	67	240	69	232	68	230	66	480	68	462	67	458	68	460	68
IIB	93	26	89	26	84	25	102	29	182	26	186	27	170	25	182	27
Risk factors‡																
Large mediastinal mass	77	22	68	20	65	19	61	17	145	21	126	18	137	21	124	18
Extranodal lesions	34	10	29	8	38	11	37	11	63	9	75	11	69	10	65	10
High ESR	192	55	172	50	166	49	183	52	364	52	349	51	347	52	343	51
≥ 3 nodal areas	232	66	239	69	224	66	246	70	471	68	470	68	441	66	470	70
Infradiaphragmatic disease	29	8	28	8	26	8	27	8	57	8	53	8	49	7	50	7
Reference histology§																
NS	211	68	218	69	222	71	219	67	429	69	441	69	421	70	430	69
MC	58	19	66	21	55	18	62	19	124	20	117	18	109	18	120	19
LP	10	3	4	1	6	2	17	5	14	2	23	4	15	3	20	3
LR	5	2	6	2	7	2	9	3	11	2	16	3	12	2	15	2
HL, not classified	22	7	15	5	20	6	18	6	37	6	38	6	38	6	31	5
Other	5	2	5	2	5	2	0	0	10	2	5	1	9	2	5	1

Abbreviations: CT, chemotherapy; RT, radiotherapy; 4×ABVD, four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; 4×BEACOPP, four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ESR, erythrocyte sedimentation rate; NS, nodular sclerosing; MC, mixed cellularity; LP, lymphocyte predominant; LR, lymphocyte rich; HL, Hodgkin's lymphoma.

*All qualified patients.

†Analysis set for RT comparison only.

‡Information missing for seven patients (four in arm A, one in arm B, and two in arm C).

§Documented for 91% of patients (n = 1,265 for treatment arm and CT comparison; n = 1,225 for RT comparison).

Baseline Characteristics

The baseline characteristics of patients were well balanced between treatment arms (Table 1). The median age of patients at random assignment was 33 years (range, 16 to 75 years); 51% of patients were female, and 49% were male. In total, 6.1% of patients had stage I disease (3.4% IA and 2.7% IB), and 93.9% had stage II disease (67.5% IIA and 26.4% IIB). Of all patients, 19.5% had bulky mediastinal mass, 9.9% had extranodal disease, 51.4% had high ESR, and 67.8% had three or more lymph node areas involved. Localized infradiaphragmatic disease was present in 7.9% of patients.

A histologic review was performed in 90.7% of patients. The most frequent histologic subtype was nodular sclerosis (68.7%), followed by mixed cellularity (19.1%).

Dose Delivery

Patients treated with the recommended four cycles of chemotherapy received a mean relative chemotherapy dose of 98.9% for ABVD and 98.3% for $BEACOPP_{baseline}$. In total, 87.0% of patients had at least 95% of the target dose (ABVD, 88.4%; $BEACOPP_{baseline}$, 85.5%). The mean relative dose-intensity was 91.7% in the ABVD arms and 94.7% in the $BEACOPP_{baseline}$ arms, suggesting that treatment delays were more frequent with ABVD.

The mean dose of radiotherapy was 30.2 Gy in the 30-Gy arms and 20.5 Gy in the 20-Gy arms. Only 3.0% of patients received a dose deviating more than 10% from the recommended dose (30 Gy, 1.8%; 20 Gy, 4.2%).

Toxicity and Supportive Measures

Acute toxicity during treatment is summarized in Table 2. Patients treated with $BEACOPP_{baseline}$ more often developed severe toxicity compared with patients receiving ABVD (WHO grade 3 or 4: 73.8% *v* 51.5%, respectively; $P < .001$). Most common adverse effects were hair loss and hematologic toxicity. G-CSF was administered in 12.6% of patients in the ABVD arms and 18.0% of patients in the $BEACOPP_{baseline}$ arms. Of these patients, the mean number of courses

Table 2. Acute and Late Effects of Treatment and Mortality

	Treatment Arm*								CT Comparison*				RT Comparison†			
	4×ABVD + 30 Gy (n = 356)		4×ABVD + 20 Gy (n = 347)		4×BEACOPP + 30 Gy (n = 341)		4×BEACOPP + 20 Gy (n = 351)		4×ABVD + RT (n = 703)		4×BEACOPP + RT (n = 692)		CT + 30 Gy (n = 675)		CT + 20 Gy (n = 676)	
Toxicity, Treatment Effects, and Mortality	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Acute toxicity‡																
At least one									358	51.5	503	73.8	75	12.0	36	5.7
Anemia									4	0.6	50	7.3	1	0.2	1	0.2
Thrombocytopenia									1	0.1	11	1.6	2	0.3	2	0.3
Leukopenia									173	24.9	262	38.4	7	1.1	4	0.6
Nausea/vomiting									105	15.1	60	8.8	9	1.4	1	0.2
Mucositis									10	1.4	14	2.1	20	3.2	10	1.6
GI tract/dysphagia									9	1.3	17	2.5	59	9.5	23	3.7
Respiratory tract									18	2.6	22	3.2	5	0.8	2	0.3
Alopecia									213	30.6	396	58.1	6	1.0	1	0.2
Infection									27	3.9	51	7.5	0	0.0	1	0.2
Pain									13	1.9	21	3.1	6	1.0	3	0.5
Nervous system									11	1.6	23	3.4	0	0.0	0	0.0
Other									18	2.6	37	5.4	11	1.8	5	0.8
Secondary neoplasia																
Total	9	2.5	19	5.5	14	4.1	10	2.8	28	4.0	24	3.5	23	3.4	27	4.0
AML/MDS	0	0.0	1	0.3	1	0.3	1	0.3	1	0.1	2	0.3	1	0.1	2	0.3
NHL	4	1.1	5	1.4	5	1.5	0	0.0	9	1.3	5	0.7	9	1.3	4	0.6
Solid tumor	5	1.4	13	3.7	8	2.3	9	2.6	18	2.6	17	2.5	13	1.9	21	3.1
Total mortality	26	7.3	30	8.6	26	7.6	23	6.6	56	8.0	49	7.1	44	6.5	42	6.2
Causes of death																
HL	7	2.0	10	2.9	10	2.9	11	3.1	17	2.4	21	3.0	14	2.1	18	2.7
Secondary neoplasia	3	0.8	8	2.3	6	1.8	2	0.6	11	1.6	8	1.2	9	1.3	9	1.3
Cardiovascular	5	1.4	3	0.9	4	1.2	2	0.6	8	1.1	6	0.9	9	1.3	4	0.6
Toxicity of study treatment	3	0.8	1	0.3	2	0.6	1	0.3	4	0.6	3	0.4	1	0.1	0	0.0
Toxicity of salvage treatment	2	0.6	1	0.3	3	0.9	2	0.6	3	0.4	5	0.7	5	0.7	3	0.4
Other	6	1.7	7	2.0	1	0.3	5	1.4	13	1.8	6	0.9	6	0.9	8	1.2

Abbreviations: CT, chemotherapy; RT, radiotherapy; 4×ABVD, four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; 4×BEACOPP, four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

*All qualified patients.

†Analysis set for RT comparison only.

‡Toxicity is defined as WHO grade 3 or 4 for CT and National Cancer Institute Common Toxicity Criteria grade 3 or 4 for RT. For CT comparison group, information is missing for 18 patients (eight in ABVD group and 10 in BEACOPP group). For RT comparison group, information is missing for 99 patients (52 in 30-Gy group and 47 in 20-Gy group).

in which G-CSF was given was 2.4 and did not differ between treatment arms. Hospitalization was more frequent with $BEACOPP_{baseline}$ than ABVD (58.8% *v* 42.6%, respectively).

More toxicity occurred in patients treated with 30 Gy of IFRT compared with 20 Gy (National Cancer Institute Common Toxicity Criteria grade 3 or 4: 12.0% *v* 5.7%, respectively; $P < .001$). During radiotherapy, the most common toxicities were dysphagia and mucositis.

Secondary Neoplasia

Fifty-two secondary neoplasias occurred, including 35 solid tumors, 14 non-Hodgkin's lymphomas, and three acute myeloid leukemias, at a median follow-up of 82 months. No differences in secondary neoplasia were observed between treatment arms or modalities (Table 2).

Mortality

With a median follow-up for survival of 91 months, a total of 105 patients (7.5%) died. Most frequent events were HL, secondary neoplasia, and cardiovascular mortality. There was no difference in terms of mortality between arms or modalities (Table 2).

Efficacy Outcomes

The overall complete response rate was 94.1%, the partial response rate was 1.1%, less than 1% of patients were nonresponders, and 2.1% of patients experienced disease progression. The relapse rate at a median follow-up of 82 months was 9.7% (Table 3).

As shown in Figure 2, OS was excellent and did not differ between the four arms of the study. FFTF and PFS were similar in arm A (four cycles of ABVD + 30 Gy of IFRT) and the $BEACOPP_{baseline}$ arms C and D, but lower in arm B (four cycles of ABVD + 20 Gy of IFRT). Because arm B included both less intensive chemotherapy and less intensive radiotherapy, these results suggest interaction effects between chemotherapy and radiotherapy. Statistical tests comparing a model with a multiplicative interaction term and a model without an interaction term failed to demonstrate significance. However, the sample size of the study did not provide sufficient statistical power to prove interaction in this way. Thus, we compared the three single experimental arms (arms B, C, and D) with the standard arm (arm A) in a different Cox regression model, together with all candidate prognostic factors. In this model, arm B was clearly inferior to the standard arm A, whereas arms C and D provided similar results to arm A. With respect to PFS, the difference between arm B and the standard arm A was significant (hazard ratio = 1.49; 95% CI, 1.04 to 2.15; $P = .03$). The FFTF analysis gave similar but nonsignificant results (hazard ratio = 1.39; 95% CI, 0.98 to 1.97; $P = .06$). All regression models are listed in Table 4. Although these tests are not completely conclusive in a strict and formal sense, they indicate relevant interaction between treatment modalities. Thus, arms were subsequently analyzed separately to avoid potentially misleading results.

FFTF, PFS, and OS rates for the single arms and estimates for differences between arms are listed in Table 5. After four cycles of $BEACOPP_{baseline}$, 20 Gy of IFRT was noninferior to 30 Gy (arm C *v* arm D; analysis set for radiotherapy comparison, n = 669; 5-year FFTF difference, −0.8%; 95% CI, −5.8% to 4.2%). In contrast, a difference of ≥ 7% between 20 Gy and 30 Gy of IFRT could not be excluded after four cycles of ABVD (arm A *v* arm B; analysis set for radiotherapy comparison, n = 682; 5-year FFTF difference, −4.7%; 95% CI, −10.3% to 0.8%).

Similar conclusions resulted from the chemotherapy comparison; if only arms A and C were compared in which 30 Gy of IFRT was given (n = 697), there was no relevant difference in FFTF between $BEACOPP_{baseline}$ and ABVD ($P = .65$). In contrast, a comparison of arms B and D (n = 698), in which 20 Gy of IFRT was given, showed a significant difference between patients treated with $BEACOPP_{baseline}$ and ABVD ($P = .02$).

DISCUSSION

In the HD11 study presented here, four cycles of ABVD or $BEACOP-P_{baseline}$ were combined with 20 or 30 Gy of IFRT to define the best

Table 3. Response and Events

Response or Event	Treatment Arm*							
	4×ABVD + 30 Gy (n = 356)		4×ABVD + 20 Gy (n = 347)		4×BEACOPP + 30 Gy (n = 341)		4×BEACOPP + 20 Gy (n = 351)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Final response†								
CR/CRu	337	94.7	322	92.8	322	94.4	332	94.6
PR	5	1.4	7	2.0	1	0.3	2	0.6
NC	1	0.3	1	0.3	0	0.0	2	0.6
Progression	5	1.4	9	2.6	10	2.9	5	1.4
Unknown	8	2.2	8	2.3	8	2.3	10	2.8
Events‡								
Progression	5	1.4	10	2.9	11	3.2	8	2.3
First relapse	33	9.3	47	13.5	24	7.0	32	9.1

Abbreviations: 4×ABVD, four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; 4×BEACOPP, four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete response; CRu, unconfirmed complete response; PR, partial response; NC, no change.

*All qualified patients.

†Final response was defined as Hodgkin's lymphoma status at final restaging 4 to 6 weeks after completion of radiotherapy; if no additional treatment was given after non-CR and there was no progression of disease within 6 months, then the final response was retrospectively redefined as CRu.

‡There were a total of 34 progressions and 136 first relapses; 23 patients had two events, and four patients had three events.

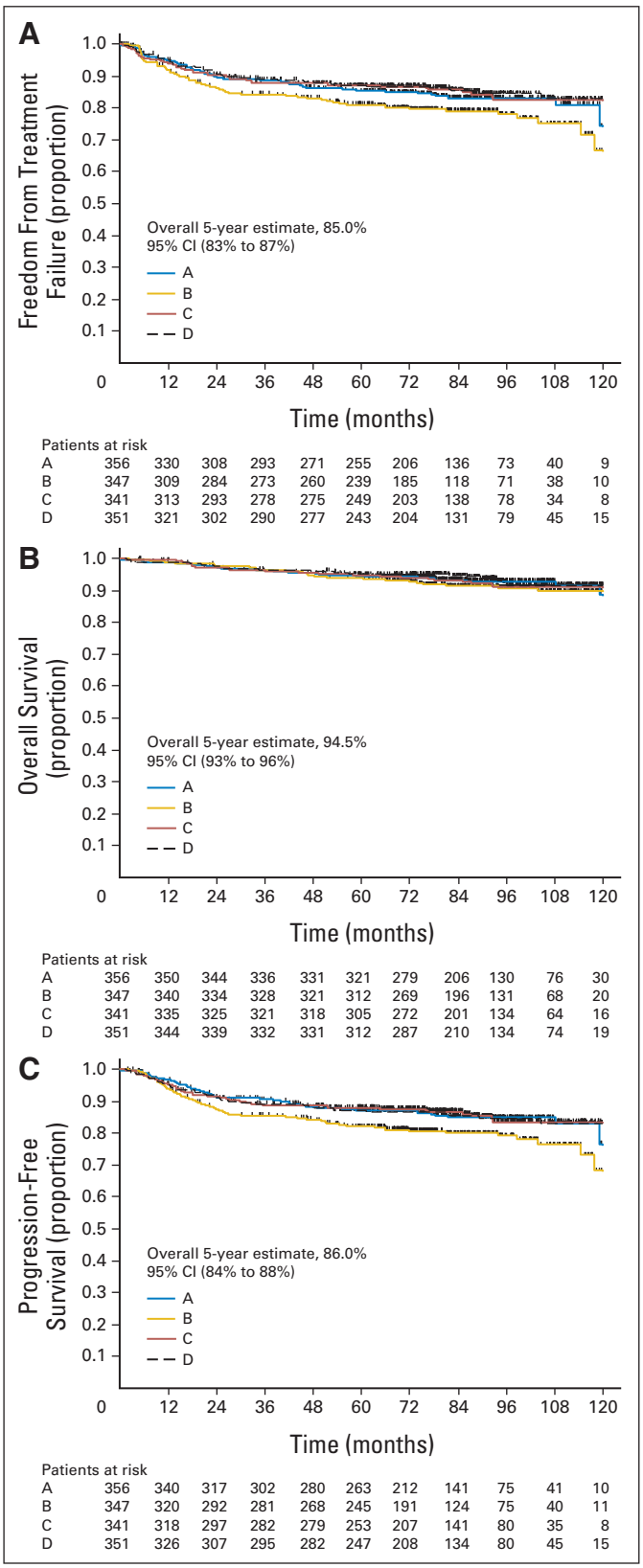

Fig 2. Kaplan-Meier curves for the four treatment arms. (A) Freedom from treatment failure, (B) overall survival, and (C) progression-free survival. Median observation time was (A) 81 months, (B) 91 months, and (C) 82 months. With respect to freedom from treatment failure and progression-free survival, treatment arm B is clearly inferior to the other treatment arms.

Table 4. Cox Regression Models

Parameter	*P*	Hazard Ratio	95% CI
Test 1: multiplicative interaction term, FFTF, CT analysis set, N = 1,395			
Sex: male	.05	1.31	1.00 to 1.71
Age, years			
50-59	.36	1.23	0.79 to 1.90
60-69	.02	1.71	1.07 to 2.74
70-75	< .001	3.43	1.76 to 6.66
Infradiaphragmal nodes	.02	1.63	1.07 to 2.48
RF mediastinal mass	< .001	1.77	1.28 to 2.46
RF high ESR	.12	1.24	0.95 to 1.64
RF extranodal involvement	.16	1.36	0.88 to 2.09
CT main effect	.01		
RT main effect	.06		
CT-RT interaction	.16		
Test 2: single-arm comparison (reference: standard arm), FFTF, CT analysis set, N = 1,395			
Sex: male	.05	1.31	1.00 to 1.71
Age, years			
50-59	.36	1.23	0.79 to 1.90
60-69	.02	1.71	1.07 to 2.74
70-75	< .001	3.43	1.76 to 6.66
Infradiaphragmal nodes	.02	1.63	1.07 to 2.48
RF mediastinal mass	< .001	1.77	1.28 to 2.46
RF high ESR	.12	1.24	0.95 to 1.64
RF extranodal involvement	.16	1.36	0.88 to 2.09
Treatment arms	.04		
Arm B: ABVD/20 Gy	.06	1.39	0.98 to 1.97
Arm C: BEACOPP/30 Gy	.66	0.92	0.63 to 1.34
Arm D: BEACOPP/20 Gy	.50	0.88	0.60 to 1.28
Test 3: single-arm comparison (reference: standard arm), PFS, CT analysis set, N = 1,395			
Sex: male	.14	1.23	0.94 to 1.62
Age, years			
50-59	.23	1.31	0.84 to 2.03
60-69	.01	1.80	1.13 to 2.87
70-75	< .001	4.04	2.13 to 7.65
Infradiaphragmal nodes	.003	1.87	1.24 to 2.81
RF mediastinal mass	.004	1.66	1.18 to 2.35
RF high ESR	.12	1.25	0.94 to 1.66
RF extranodal involvement	.13	1.40	0.90 to 2.18
Treatment arms	.04		
Arm B: ABVD/20 Gy	.03	1.49	1.04 to 2.15
Arm C: BEACOPP/30 Gy	.90	0.97	0.66 to 1.45
Arm D: BEACOPP/20 Gy	.93	0.98	0.66 to 1.46

Abbreviations: FFTF, freedom from treatment failure; CT, chemotherapy; RF, risk factors; ESR, erythrocyte sedimentation rate; RT, radiotherapy; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; PFS, progression-free survival.

treatment for patients with early unfavorable HL. This final analysis shows that four cycles of ABVD + 30 Gy of IFRT leads to equivalent results as four cycles of $BEACOPP_{baseline}$ followed by either 30 or 20 Gy of IFRT. However, four cycles of ABVD followed by 20 Gy of IFRT were inferior to the other three arms, implying that a reduction of IFRT dose from 30 to 20 Gy is only possible when combined with a more intensive chemotherapy regimen than ABVD.

Earlier clinical trials highlighted the need for effective chemotherapy in patients with early unfavorable HL.[2,8,9] In contrast to early

Table 5. Survival and Differences in Survival

Treatment Arm	No. of Patients	5-Year FFTF Rate		5-Year OS Rate		5-Year PFS Rate	
		%	95% CI	%	95% CI	%	95% CI
Survival rate							
4×ABVD + 30 Gy	356	85.3	81 to 89	94.3	91 to 96	87.2	83 to 90
4×ABVD + 20 Gy	347	81.1	76 to 85	93.8	91 to 96	82.1	78 to 86
4×BEACOPP + 30 Gy	341	87.0	83 to 90	94.6	92 to 97	87.9	84 to 91
4×BEACOPP + 20 Gy	351	86.8	83 to 90	95.1	92 to 97	87.0	83 to 90
Difference in survival rates							
4×ABVD + 30 Gy *v* 4×BEACOPP + 30 Gy*	697	1.6	−3.6 to 6.9	0.3	−3.2 to 3.8	0.7	−4.3 to 5.8
4×ABVD + 20 Gy *v* 4×BEACOPP + 20 Gy*	698	5.7	0.1 to 11.3	1.2	−2.3 to 4.8	4.9	−0.6 to 10.4
4×ABVD + 30 Gy *v* 4×ABVD + 20 Gy†	682	−4.7	−10.3 to 0.8	−0.7	−4.1 to 2.8	−4.7	−10.1 to 0.8
4×BEACOPP + 30 Gy *v* 4×BEACOPP + 20 Gy†	669	−0.8	−5.8 to 4.2	1.0	−2.1 to 4.0	−0.6	−5.5 to 4.3

Abbreviations: FFTF, freedom from treatment failure; OS, overall survival; PFS, progression-free survival; 4×ABVD, four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; 4×BEACOPP, four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.
*All qualified patients.
†Analysis set for radiotherapy comparison only.

favorable HL, less toxic regimens such as epirubicin, bleomycin, vinblastine, and prednisone were not as effective as mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine chemotherapy in this setting.[1] Subsequently, ABVD became the standard of care for this group of patients. However, failure rates of up to 20% warranted further improvement and formed the rationale for the HD11 trial. The choice of $BEACOPP_{baseline}$ was based on the higher effective dose of this regimen compared with ABVD and the superior outcome of $BEACOPP_{baseline}$ when compared directly with ABVD-containing regimens in advanced-stage HL.[5]

A similar trial to HD11 was conducted by the European Organisation for Research and Treatment of Cancer–Groupe d'Etude des Lymphomes de l'Adulte (EORTC-GELA). In their H9U study, the standard arm of six cycles of ABVD followed by 30 Gy of IFRT was compared with four cycles of ABVD or four cycles of $BEACOPP_{baseline}$; IFRT was fixed at 30 Gy. In line with our results, the interim analysis also indicated no differences in response, event-free survival, or OS among the three treatment arms.[10] Chemotherapy-related toxicity in H9U was higher with $BEACOPP_{baseline}$ compared with ABVD, similar to the present study. In our HD11 study, patients treated with $BEACOPP_{baseline}$ more often developed severe toxicity than patients treated with ABVD (73.8% *v* 51.5%, respectively; $P < .001$).

Overall, more severe toxicity occurred in patients treated with 30 Gy of IFRT compared with 20 Gy (12.0% *v* 5.7%, respectively; $P < .001$). This was also true for the GHSG parallel trial conducted in patients with early favorable HL (HD10). In that trial, patients treated with two or four cycles of ABVD experienced a grade 3 or 4 toxicity rate of 8.7% after 30 Gy of IFRT compared with a rate of 2.9% in patients treated with 20 Gy ($P < .001$). In contrast to the unfavorable group, however, a reduction of radiation dose from 30 to 20 Gy was feasible and safe in patients with early favorable HL even after two courses of ABVD.[11] Another alternative to diminish radiation-induced toxicity is the reduction of field size beyond IFRT. The EORTC-GELA group recently introduced the new involved-node radiotherapy (INRT) concept into the combined-modality treatment of early HL. Here, radiotherapy is confined only to initially involved lymph nodes with an additional small isotropic margin.[12-14] The development of INRT was in part based on the finding that recurrences in patients treated with chemotherapy alone typically occur in sites of initial nodal involvement. This technique should result in less normal tissue receiving unnecessary radiation.[15] INRT is being evaluated in the ongoing EORTC-GELA and GHSG randomized trials H10U and HD17 for patients with early unfavorable HL.

The concept of dose escalation in the early unfavorable group of patients with HL was further pursued in the GHSG follow-up study (HD14). Here, two cycles of the more aggressive $BEACOPP_{escalated}$ regimen were followed by two cycles of ABVD (2+2) and 30 Gy of IFRT. The latest interim results with a total of 1,127 patients analyzed indicated a significantly better tumor control for 2+2 compared with four cycles of ABVD (97% *v* 91%, respectively), resulting in early termination of this trial and the use of 2+2 as new standard in the GHSG HD17 follow-up study.[16] Although the 6% better PFS in HD14 still has to be carefully balanced against more toxicity with the 2+2 combination, this study is a clear proof of concept for dose intensification in early unfavorable HL. For now, however, neither four cycles of $BEACOPP_{baseline}$ as in HD11 nor 2+2 should be regarded as standard of care for early unfavorable HL outside clinical trials.

HD11 demonstrates that even a modestly more effective chemotherapy allows for reduction in the radiotherapy dose needed in this setting. Thus, major questions for future studies involve finding the optimal balance between chemotherapy and radiotherapy intensity. How much additional toxicity as a result of more intensive chemotherapy is acceptable? Will it be possible to delete radiotherapy in good-risk early unfavorable HL? Clinical risk factors established for advanced stages[17] do not allow reliable response prediction in this setting.[18] To this end, the use of positron emission tomography (PET) might facilitate discriminating between good- and poor-risk patients, both early in the course of treatment[19] and after chemotherapy.[20] The potential impact of PET in patients with HL has also been suggested by a number of retrospective nonrandomized studies.[21,22] In both early favorable and early unfavorable HL, currently ongoing trials are evaluating the role of PET in identifying patients who might not need additional RT after two to four cycles of initial chemotherapy. In summary, the HD11 trial presented here demonstrated that four cycles of $BEACOPP_{baseline}$ were more toxic and equally effective as four cycles of ABVD and that ABVD needs to be combined with 30 Gy of IFRT in patients with early unfavorable HL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Hans Theodor Eich, Peter Borchmann, Rolf-Peter Müller, Andreas Engert
Provision of study materials or patients: Thomas Pabst, Peter Borchmann, Andreas Engert
Collection and assembly of data: Hans Theodor Eich, Jana Markova, Jürgen Debus, Anthony Ho, Bernd Dörken, Andreas Rank, Anca-Ligia Grosu, Thomas Wiegel, Johann Hinrich Karstens, Richard Greil, Normann Willich, Heinz Schmidberger, Hartmut Döhner, Peter Borchmann, Andreas Engert
Data analysis and interpretation: Hans Theodor Eich, Helen Görgen
Manuscript writing: Hans Theodor Eich, Helen Görgen, Andreas Engert
Final approval of manuscript: Hans Theodor Eich, Volker Diehl, Helen Görgen, Thomas Pabst, Jana Markova, Jürgen Debus, Anthony Ho, Bernd Dörken, Andreas Rank, Anca-Ligia Grosu, Thomas Wiegel, Johann Hinrich Karstens, Richard Greil, Normann Willich, Heinz Schmidberger, Hartmut Döhner, Peter Borchmann, Hans-Konrad Müller-Hermelink, Rolf-Peter Müller, Andreas Engert

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