ORIGINAL ARTICLE

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Whether it is possible to reduce the intensity of treatment in early (stage I or II) Hodgkin's lymphoma with a favorable prognosis remains unclear. We therefore conducted a multicenter, randomized trial comparing four treatment groups consisting of a combination chemotherapy regimen of two different intensities followed by involved-field radiation therapy at two different dose levels.

METHODS

We randomly assigned 1370 patients with newly diagnosed early-stage Hodgkin's lymphoma with a favorable prognosis to one of four treatment groups: four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30 Gy of radiation therapy (group 1), four cycles of ABVD followed by 20 Gy of radiation therapy (group 2), two cycles of ABVD followed by 30 Gy of radiation therapy (group 3), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4). The primary end point was freedom from treatment failure; secondary end points included efficacy and toxicity of treatment.

RESULTS

The two chemotherapy regimens did not differ significantly with respect to freedom from treatment failure (P=0.39) or overall survival (P=0.61). At 5 years, the rates of freedom from treatment failure were 93.0% (95% confidence interval [CI], 90.5 to 94.8) with the four-cycle ABVD regimen and 91.1% (95% CI, 88.3 to 93.2) with the two-cycle regimen. When the effects of 20-Gy and 30-Gy doses of radiation therapy were compared, there were also no significant differences in freedom from treatment failure (P=1.00) or overall survival (P=0.61). Adverse events and acute toxic effects of treatment were most common in the patients who received four cycles of ABVD and 30 Gy of radiation therapy (group 1).

CONCLUSIONS

In patients with early-stage Hodgkin's lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Long-term effects of these treatments have not yet been fully assessed. (Funded by the Deutsche Krebshilfe and the Swiss Federal Government; ClinicalTrials.gov number, NCT00265018.)

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Radiation therapy was the original mainstay of treatment for patients who had early-stage Hodgkin's lymphoma with a favorable prognosis. With the use of such techniques as extended-field radiation therapy and total lymphoid irradiation, more than 80% of patients with localized disease became long-term survivors. However, the relapse rate with radiation therapy alone ranged from 20 to 40%,[1-3] and extended-field radiation therapy and total lymphoid irradiation were associated with the occurrence of secondary solid tumors.[4-8] The integration of a chemotherapy regimen consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)[9] with radiation therapy resulted in greater efficacy and allowed the radiation field and dose to be reduced, leading to widespread use of the combined approaches in patients with early-stage Hodgkin's lymphoma and a favorable prognosis.[10,11] Four cycles of ABVD followed by 30 Gy of involved-field radiation therapy is now regarded as the standard of care by many groups.[11-14] The use of chemotherapy alone has been considered as a potential alternative approach but remains controversial.[15-19]

Whether the number of treatment cycles and the radiation dose can be reduced in patients with early-stage Hodgkin's lymphoma and a favorable prognosis remains unclear. In an attempt to reduce the toxic effects of treatment while retaining full control of the cancer, the German Hodgkin Study Group (GHSG) in 1998 initiated a prospective, randomized, multicenter study (HD10) in which four cycles of ABVD chemotherapy were compared with two cycles of ABVD, and 30 Gy of involved-field radiation therapy was compared with 20 Gy of involved-field radiation therapy in patients receiving either of the two chemotherapy regimens.

Methods

Study Patients

We enrolled patients who had newly diagnosed Hodgkin's lymphoma in clinical stage I or II, as confirmed on histologic examination, with no clinical risk factors. Patients were eligible if they were between 16 and 75 years of age, had not been treated previously for Hodgkin's lymphoma, and were free of concurrent disease. (Details regarding the definitions of clinical risk factors and full descriptions of the inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Study Design

HD10 was a multicenter, randomized study of four different treatment regimens in patients with early-stage Hodgkin's lymphoma and a favorable diagnosis. Patients were recruited and treated at 329 hospitals and outpatient practices in Germany, Switzerland, the Netherlands, the Czech Republic, and Austria. After clinical staging had been completed and written informed consent obtained, patients were registered at the GHSG central trial office by telephone and then randomly assigned in a 1:1:1:1 ratio to one of four treatment groups: group 1 received four cycles of ABVD followed by 30 Gy of involved-field radiation therapy; group 2 received four cycles of ABVD followed by 20 Gy of involved-field radiation therapy; group 3 received two cycles of ABVD followed by 30 Gy of involved-field radiation therapy; and group 4 received two cycles of ABVD followed by 20 Gy of involved-field radiation therapy.

Stratification factors included trial center and prognostic factors that might influence the primary end point, such as age (<50 vs. ≥50 years), systemic symptoms, supradiaphragmatic or infradiaphragmatic disease, and albumin level (<4 vs. ≥4 g per deciliter). A 2-by-2 factorial design was chosen: for the chemotherapy comparison, the results in groups 1 and 2, which received four cycles of ABVD, were pooled, as were the results in groups 3 and 4, which received two cycles of ABVD. Similarly, for the radiation therapy comparison, the results in groups 1 and 3, which received the 30-Gy dose of involved-field radiation therapy, were pooled and compared with the results in groups 2 and 4, which received the 20-Gy dose of involved-field radiation therapy.

The HD10 protocol was designed by the GHSG steering committee and approved by the ethics committees of the participating centers. The study was performed in accordance with the protocol. An independent data and safety monitoring committee monitored the patients' safety and the efficacy of treatment throughout the 5-year study period. The GHSG central trial office was responsible for data collection, data management, and statistical analyses, as well as for internal presentations of results to the GHSG chairman and participating centers. The GHSG steering committee and chair decided to submit the results of the final analysis for publication. All authors contrib-

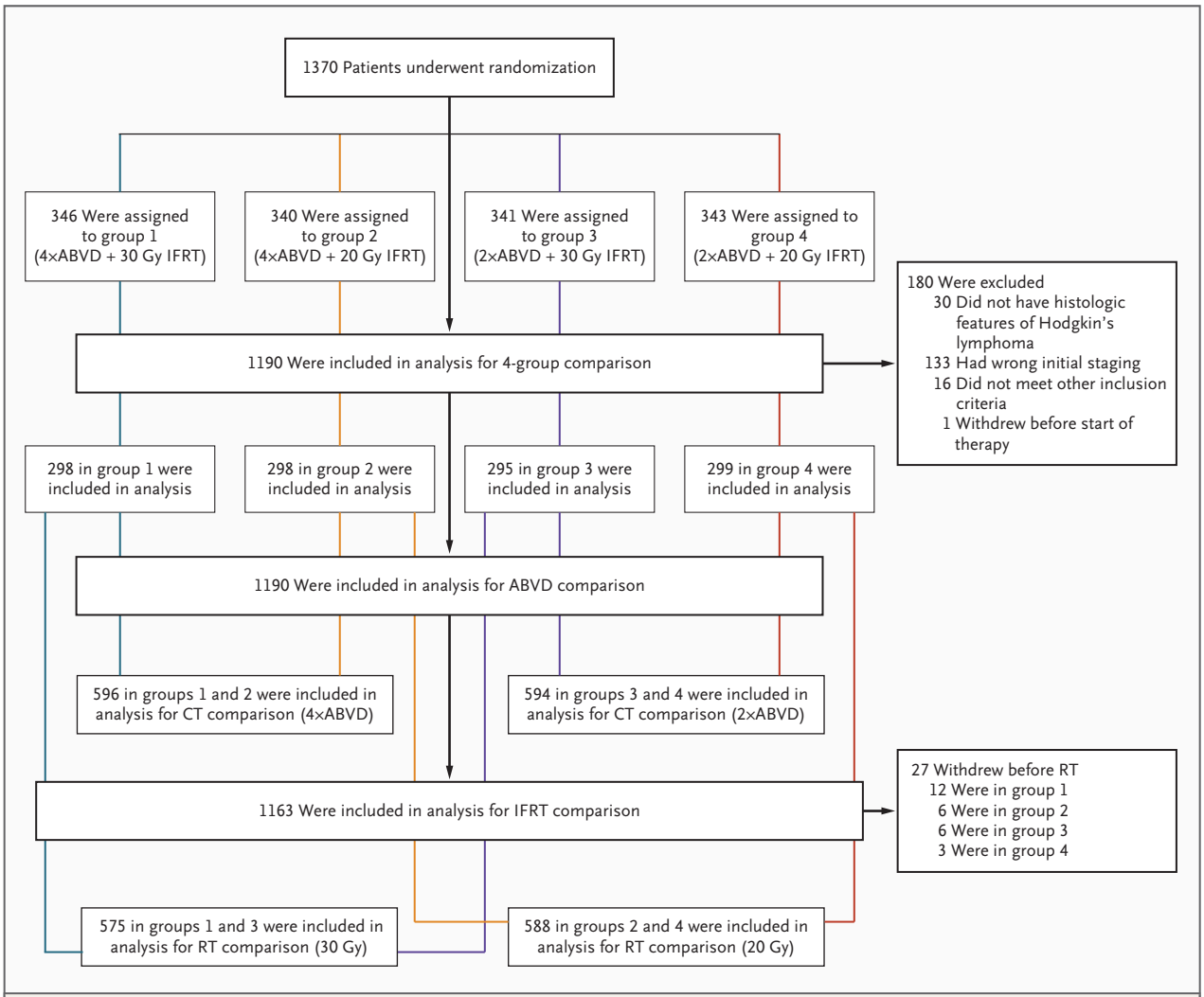


Figure 1. Numbers of Patients Randomly Assigned to Treatment Groups and Included in Analyses.
ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, and IFRT involved-field radiation therapy.

uted to the interpretation of the results and vouch for the accuracy and completeness of the data. The GHSG chair wrote the first draft of the manuscript and was supported by the lead statistician. There was no commercial involvement in this study and no financial support from industry.

CHEMOTHERAPY

ABVD was administered on days 1 and 15 in monthly cycles, at the following standard doses: doxorubicin, 25 mg per square meter of body-surface area; bleomycin, 10 mg per square meter; vinblastine, 6 mg per square meter; and dacarbazine, 375 mg per square meter. If the white-cell count was less than 2500 per cubic millimeter or the platelet count was less than 80,000 per cubic millimeter on a day when chemotherapy was scheduled to be administered, treatment was postponed until normal levels were achieved. Granulocyte colony-stimulating factor was given if clinically indicated.

RADIATION THERAPY

Before treatment, all sites of disease were defined and documented by the treating medical oncologist and radiation oncologist. A central panel of experts in radiation oncology then planned involved-field radiation therapy as defined in the study protocol according to treatment group and, if necessary, revised the initial staging. The rec-

Table 1. Baseline Characteristics of the Patients According to Treatment Group.*

Characteristic		Treatment Group†				Chemotherapy Comparison		Radiation Therapy Comparison	
	All Patients (N=1190)	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
Age — yr	38.8±14.3	39.5±14.2	38.6±14.5	38.3±14.3	38.7±14.4	39.0±14.3	38.5±14.3	38.6±13.9	38.6±14.4
Female sex — no. (%)	465 (39.1)	116 (38.9)	121 (40.6)	106 (35.9)	122 (40.8)	236 (39.6)	228 (38.4)	215 (37.4)	239 (40.6)
Ann Arbor stage — no. (%)‡									
IA	361 (30.3)	94 (31.5)	92 (30.9)	99 (33.6)	76 (25.4)	186 (31.2)	175 (29.5)	188 (32.7)	166 (28.2)
IB	24 (2.0)	5 (1.7)	6 (2.0)	7 (2.4)	6 (2.0)	11 (1.8)	13 (2.2)	12 (2.1)	12 (2.0)
IIA	738 (62.0)	182 (61.1)	184 (61.7)	175 (59.3)	197 (65.9)	366 (61.4)	372 (62.6)	346 (60.2)	375 (63.8)
IIB	66 (5.5)	17 (5.7)	15 (5.0)	14 (4.7)	20 (6.7)	32 (5.4)	34 (5.7)	29 (5.0)	35 (6.0)
Infradiaphragmatic disease — no. (%)	97 (8.2)	25 (8.4)	26 (8.7)	21 (7.1)	25 (8.4)	50 (8.4)	46 (7.7)	44 (7.7)	49 (8.3)
Histologic type of Hodgkin's lymphoma — no. of patients/total no. (%)§									
Nodular lymphocyte-predominant	81/1080 (7.5)	20/273 (7.3)	17/263 (6.5)	24/272 (8.8)	20/272 (7.4)	37/535 (6.9)	44/544 (8.1)	43/528 (8.1)	35/526 (6.7)
Lymphocyte-rich classic	98/1080 (9.1)	23/273 (8.4)	19/263 (7.2)	35/272 (12.9)	21/272 (7.7)	42/535 (7.9)	56/544 (10.3)	58/528 (11.0)	40/526 (7.6)
Nodular sclerosing	420/1080 (38.9)	101/273 (37.0)	112/263 (42.6)	98/272 (36.0)	109/272 (40.1)	213/535 (39.8)	207/544 (38.1)	197/528 (37.3)	219/526 (41.6)
Mixed cellularity	435/1080 (40.3)	118/273 (43.2)	103/263 (39.2)	99/272 (36.4)	115/272 (42.3)	220/535 (41.1)	214/544 (39.3)	206/528 (39.0)	213/526 (40.5)
Lymphocyte-depleted	1/1080 (0.1)	0	0	1/272 (0.4)	0	0	1/544 (0.2)	1/528 (0.2)	0
Not classified	45/1080 (4.2)	11/273 (4.0)	12/263 (4.6)	15/272 (5.5)	7/272 (2.6)	23/535 (4.3)	22/544 (4.0)	23/528 (4.4)	19/526 (3.6)

* Plus–minus signs are means ±SD. ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, and IFRT involved-field radiation therapy.
† These groups include all eligible patients.
‡ Information on stage of disease was missing for 1 patient in group 2.
§ Information on histologic subtype was available for 1080 patients (90.7%).

Table 2. Adverse Events According to Treatment Group.

Event	Treatment Group*				Chemotherapy Comparison		Radiation Therapy Comparison	
	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
	number of patients (percent)				*no. of patients/total no. (%)*			
Acute toxicity (grade III or IV)†								
At least one event					304/588 (51.7)	194/585 (33.2)	46/528 (8.7)	16/553 (2.9)
Anemia					7/588 (1.2)	1/585 (0.2)	0	0
Thrombopenia					3/588 (0.5)	0	0	0
Leukopenia					138/588 (23.5)	87/585 (14.9)	0	0
Nausea or vomiting					79/588 (13.4)	51/585 (8.7)	3/528 (0.6)	6/553 (1.1)
Mucositis					7/588 (1.2)	2/585 (0.3)	18/528 (3.4)	4/553 (0.7)
Gastrointestinal tract disorder or dysphagia					11/588 (1.9)	6/585 (1.0)	30/528 (5.7)	16/553 (2.9)
Respiratory tract disorder					12/588 (2.0)	2/585 (0.3)	2/528 (0.4)	0
Hair loss					165/588 (28.1)	89/585 (15.2)	6/528 (1.1)	3/553 (0.5)
Infection					30/588 (5.1)	10/585 (1.7)	1/528 (0.2)	0
Pain					9/588 (1.5)	14/585(2.4)	3/528 (0.6)	1/553 (0.2)
Nervous system disorder					12/588 (2.0)	7/585 (1.2)	2/528 (0.4)	0
Secondary neoplasia‡								
Total	17 (5.7)	10 (3.4)	14 (4.7)	14 (4.7)	27 (4.5)	28 (4.7)	31 (5.4)	24 (4.1)
Acute myelocytic leukemia or myelodysplastic syndrome	2 (0.7)	0	0	0	2 (0.3)	0	2 (0.3)	0
Non–Hodgkin's lymphoma	4 (1.3)	3 (1.0)	3 (1.0)	5 (1.7)	7 (1.2)	8 (1.3)	7 (1.2)	8 (1.4)
Solid tumor	11 (3.7)	7 (2.3)	11 (3.7)	9 (3.0)	18 (3.0)	20 (3.4)	22 (3.8)	16 (2.7)

Death‡								
Total no. of deaths	15 (5.0)	13 (4.4)	16 (5.4)	13 (4.3)	28 (4.7)	29 (4.9)	25 (4.3)	22 (3.7)
Cause of death								
Hodgkin's lymphoma	3 (1.0)	2 (0.7)	3 (1.0)	2 (0.7)	5 (0.8)	5 (0.8)	5 (0.9)	3 (0.5)
Toxicity of primary therapy	3 (1.0)	3 (1.0)	1 (0.3)	0	6 (1.0)§	1 (0.2)§	1 (0.2)	0
Toxicity of salvage therapy	0	0	4 (1.4)	1 (0.3)	0	5 (0.8)	3 (0.5)	0
Secondary neoplasia	3 (1.0)	0	5 (1.7)	3 (1.0)	3 (0.5)	8 (1.3)	8 (1.4)	3 (0.5)
Cardiovascular disorder	3 (1.0)	3 (1.0)	0	3 (1.0)	6 (1.0)	3 (0.5)	3 (0.5)	6 (1.0)

* These groups include all eligible patients.
† Information on the toxicity of primary chemotherapy (World Health Organization grade III or IV) was available for 1173 of 1190 patients (98.6%). Information on the toxicity of primary involved-field radiation therapy (IFRT) (Common Toxicity Criteria grade III or IV) was available for 1081 of 1163 patients (92.9%).
‡ A total of 57 of 1190 patients died (4.8%), and 55 of 1190 patients had a secondary neoplasm (4.6%). Median observation times were 91 months for overall survival and 79 months for freedom from treatment failure and progression-free survival; 884 patients (74.3%) were followed for at least 5 years after the end of therapy.
§ Causes of treatment-related deaths were pulmonary fibrosis, probably bleomycin-induced (in two patients assigned to four cycles of ABVD and one assigned to two cycles); sepsis (in two patients assigned to four cycles of ABVD); pneumonia (in one patient assigned to four cycles of ABVD); and not specified (in one patient assigned to four cycles of ABVD).

ommended interval between completion of the ABVD regimen and the start of radiation therapy was 4 to 6 weeks. Patients received either 30 Gy or 20 Gy of involved-field radiation therapy in single fractions of 1.8 to 2.0 Gy administered five times weekly.

STUDY END POINTS

The primary efficacy end point was freedom from treatment failure. Overall survival, progression-free survival, complete response, and treatment toxicity were secondary end points. Definitions of the study end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Proof of the noninferiority of the less intensive treatment, as compared with the standard treatment of four cycles of ABVD plus 30 Gy of involved-field radiation therapy, with respect to freedom from treatment failure at 5 years was the goal for both chemotherapy and radiation therapy. The noninferiority margin was defined as 7% in the study protocol. This led to the following two hypotheses: for chemotherapy, the 5-year rate of freedom from treatment failure in the two pooled groups assigned to two cycles of ABVD would be less than 7% below the rate in the two pooled groups assigned to four cycles, and for radiation therapy, the 5-year rate of freedom from treatment failure in the two pooled groups assigned to 20 Gy of involved-field radiation therapy would be less than 7% below the rate in the two pooled groups assigned to 30 Gy.

Survival rates for the four groups were compared with the use of the Kaplan–Meier method as well as stratified Cox regression analyses for hazard ratios (i.e., the chemotherapy comparison was stratified according to the radiation therapy assignment and vice versa), whereas outcomes and toxicity rates were compared with the use of Fisher's exact test. Tests of the hypotheses were performed according to the intention-to-treat principle and also on the basis of the treatment actually received. Subgroup analyses were not prespecified in the statistical-analysis plan, but we performed post hoc sensitivity analyses that excluded patients with nodular lymphocyte-predominant Hodgkin's lymphoma. The results of these sensitivity analyses are presented in the Supplementary Appendix.

In addition, to estimate the combined effect of reduced chemotherapy and reduced radiation therapy, we compared group 1, which received the most intensive therapy, with group 4, which received the

least intensive therapy. To detect a possible influence of prognostic factors or interactions between the effects of chemotherapy and those of radiation therapy, multivariate Cox regression analyses were specified in the protocol and performed as sensitivity analyses on the same data sets for comparing the two chemotherapy regimens and the two radiation therapy regimens.

RESULTS

PATIENTS

From May 1998 through January 2003, a total of 1370 patients were recruited and randomly assigned to treatment centrally. A total of 180 patients were excluded from all analyses: 30 because the reference histologic findings did not confirm Hodgkin's lymphoma, 133 because of incorrect initial staging, 16 because they did not meet other inclusion criteria, and 1 who met the inclusion criteria but could not subsequently be contacted (Fig. 1).

The baseline characteristics of the study patients are shown in Table 1. No significant differences were noted among the treatment groups for any of the characteristics shown. The median age of patients at randomization was 36 years (range, 16 to 75), and 61.0% were male; 30.3% had stage IA disease, 2.0% had stage IB, 62.0% had stage IIA, and 5.5% had stage IIB. (Information on stage of disease was missing for one patient in group 2.) The most frequent subtype diagnosed by the pathology reference panel was mixed cellularity (40.2%), and 8.1% of patients had infradiaphragmatic disease.

The main (intention-to-treat) analysis set for the initial chemotherapy comparison (CT1) comprised 1190 patients: 596 patients were randomly assigned to four cycles of ABVD and 594 to two cycles. Of these patients, 36 changed chemotherapy group or had major protocol violations; chemotherapy was not documented for 10 patients. The per-protocol analysis set for the chemotherapy comparison (CT2) therefore comprised 1144 patients (571 randomly assigned to four cycles of ABVD and 573 to two cycles). The main (intention-to-treat) analysis set for the radiation therapy comparison (RT1) included 1163 patients: 575 patients were randomly assigned to 30 Gy of involved-field radiation therapy and 588 to 20 Gy of involved-field radiation therapy. Of these patients, 33 had a change in the radiation therapy dose or had major protocol violations; radiation therapy documentation was missing for 17 patients. The per-protocol analysis set for the radiation therapy comparison included 1113 patients (557 in the 30-Gy groups and 556 in the 20-Gy groups). There were more protocol violations and group changes in the groups that received 20 Gy of involved-field radiation therapy than in those that received 30 Gy ($P=0.05$). However, since the per protocol analysis and the intention-to-treat analysis had similar results, these imbalances did not affect the final conclusions.

ADVERSE EVENTS

Toxicity of Treatment

Acute toxicity during chemotherapy was more frequent in patients who received four cycles of ABVD than in those who received two cycles (Table 2). Overall, 51.7% of the patients who received four cycles of ABVD had at least one instance of severe toxicity (grade III or IV) as compared with 33.2% of those who received two cycles ($P<0.001$). The most frequent events were hair loss (in 28.1% of patients receiving four cycles vs. 15.2% of those receiving two cycles) and hematologic toxic effects (24.0% vs. 15.0%). Infections were also more common with four cycles of ABVD than with two cycles (5.1% vs. 1.7%). Treatment-related deaths occurred in six patients treated with four cycles of ABVD (two died from pulmonary fibrosis, two from sepsis, one from pneumonia, and one from an unspecified cause) and in one patient treated with two cycles (from pulmonary fibrosis).

Severe toxicity (grade III or IV) was observed more often among the patients treated with 30 Gy of involved-field radiation therapy than among those who received 20 Gy (8.7% vs. 2.9%, $P<0.001$).

Secondary Neoplasia

Over a median follow-up period of 7.5 years (90 months), secondary cancers were diagnosed in a total of 55 patients (4.6%): 38 solid tumors, 15 cases of non-Hodgkin's lymphoma, and 2 cases of acute myeloid leukemia. There were no significant differences in the occurrence of secondary cancers among the four treatment groups ($P=0.59$), the pooled chemotherapy groups ($P=0.89$), or the pooled radiation therapy groups ($P=0.34$).

Table 3. Efficacy Outcomes According to Treatment Group.

Outcome	Treatment Group				Chemotherapy Comparison		Radiation Therapy Comparison	
	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
Response — no. of patients (%)*								
Complete remission with or without residual radiologic abnormalities	287 (96.3)	288 (96.6)	287 (97.3)	288 (96.3)	575 (96.5)	575 (96.8)	569 (99.0)	573 (97.4)
Partial remission	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)	4 (0.7)	4 (0.7)	4 (0.7)	3 (0.5)
No change	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Progression	0	1 (0.3)	3 (1.0)	2 (0.7)	1 (0.2)	5 (0.8)	0	1 (0.2)
Unknown	8 (2.7)	7 (2.3)	2 (0.7)	7 (2.3)	15 (2.5)	9 (1.5)	1 (0.2)	10 (1.7)
First relapse†	15 (5.0)	16 (5.4)	21 (7.1)	19 (6.4)	31 (5.2)	40 (6.7)	34 (5.9)	35 (6.0)
Survival rate — % (95% CI)‡								
At 5 years								
Overall survival	96.9 (94.2–98.4)	97.3 (94.6–98.6)	96.6 (93.7–98.1)	96.6 (93.7–98.1)	97.1 (95.4–98.2)	96.6 (94.7–97.8)	97.7 (96.1–98.7)	97.5 (95.9–98.5)
Freedom from treatment failure	92.8 (89.1–95.3)	93.1 (89.4–95.5)	90.9 (86.8–93.8)	91.2 (87.1–94.1)	93.0 (90.5–94.8)	91.1 (88.3–93.2)	93.4 (91.0–95.2)	92.9 (90.4–94.8)
Progression-free survival	93.9 (90.3–96.2)	93.2 (89.5–95.6)	90.8 (86.7–93.7)	91.6 (87.6–94.4)	93.5 (91.1–95.3)	91.2 (88.5–93.4)	93.7 (91.3–95.5)	93.2 (90.6–95.0)
At 8 years								
Overall survival	94.4 (90.2–96.8)	94.7 (90.9–97.0)	93.6 (89.6–96.1)	95.1 (91.7–97.2)	94.6 (92.0–96.4)	94.4 (91.9–96.1)	94.9 (92.2–96.6)	95.6 (93.2–97.1)
Freedom from treatment failure	87.2 (81.3–91.4)	89.9 (85.2–93.1)	85.5 (79.5–89.8)	85.9 (80.2–90.1)	88.4 (84.8–91.3)	85.7 (81.8–88.9)	87.8 (83.8–90.9)	88.6 (85.1–91.3)
Progression-free survival	88.4 (82.6–92.4)	90.0 (85.4–93.2)	85.4 (79.4–89.8)	86.5 (80.9–90.6)	89.1 (85.5–91.8)	86.0 (82.1–89.1)	88.1 (84.1–91.2)	88.9 (85.4–91.6)

* The final response is generally defined as the status of Hodgkin's lymphoma at the time of final restaging, 4 to 6 weeks after the patient has completed radiation therapy; if the patient does not have a complete remission, no further treatment is given, and there is no progression of disease within 6 months, the final response is retrospectively redefined as complete remission with residual radiologic abnormalities. CI denotes confidence interval.

† There were 6 cases of progression and 71 first relapses; 3 patients had 2 relapses each, and 1 patient had 3 relapses.

‡ Median observation times were 91 months for overall survival and 79 months for freedom from treatment failure and progression-free survival; 884 patients (74.3%) were followed for at least 5 years after the end of therapy.

Deaths

A total of 57 patients (4.8%) died during the follow-up period. The most frequent causes of death were secondary neoplasia (in 11), Hodgkin's lymphoma (in 10), cardiovascular events (in 9), toxicity of primary therapy (in 7), and toxicity of salvage therapy (in 5, all after having received two cycles of ABVD). No difference in mortality was noted among the four groups or between the combined chemotherapy groups and the combined radiation therapy groups (Table 2).

DISEASE CONTROL AND SURVIVAL

Final treatment outcomes were as follows: 1150 of 1190 patients (96.6%) had a complete remission, 8 (0.7%) had a partial remission, and 8 (0.7%) did not have a response (2 had no change and 6 had progression of disease during treatment). (Response criteria are described in the Supplementary Appendix.) For 24 patients (2.0%), the treatment outcome was unclear. The relapse rate was 6.0% (71 of 1190 patients). No significant differences were seen in rates of remission, progression, or relapse among the four treatment groups or between the combined chemotherapy groups and the combined radiation therapy groups.

The rates of freedom from treatment failure in the whole intention-to-treat analysis set of 1190 patients were estimated to be 92.0% (95% confidence interval [CI], 90.2 to 93.5) at 5 years and 87.1% (95% CI, 84.5 to 89.3) at 8 years. The overall survival rates for all 1190 patients were estimated to be 96.8% (95% CI, 95.7 to 97.7) at 5 years and 94.5% (95% CI, 92.8 to 95.8) at 8 years (Table 3). For the same patients, the rate of progression-free survival was estimated to be 92.4% (95% CI, 90.6 to 93.8) at 5 years and 87.6% (95% CI, 85.0 to 89.7) at 8 years.

CHEMOTHERAPY COMPARISON

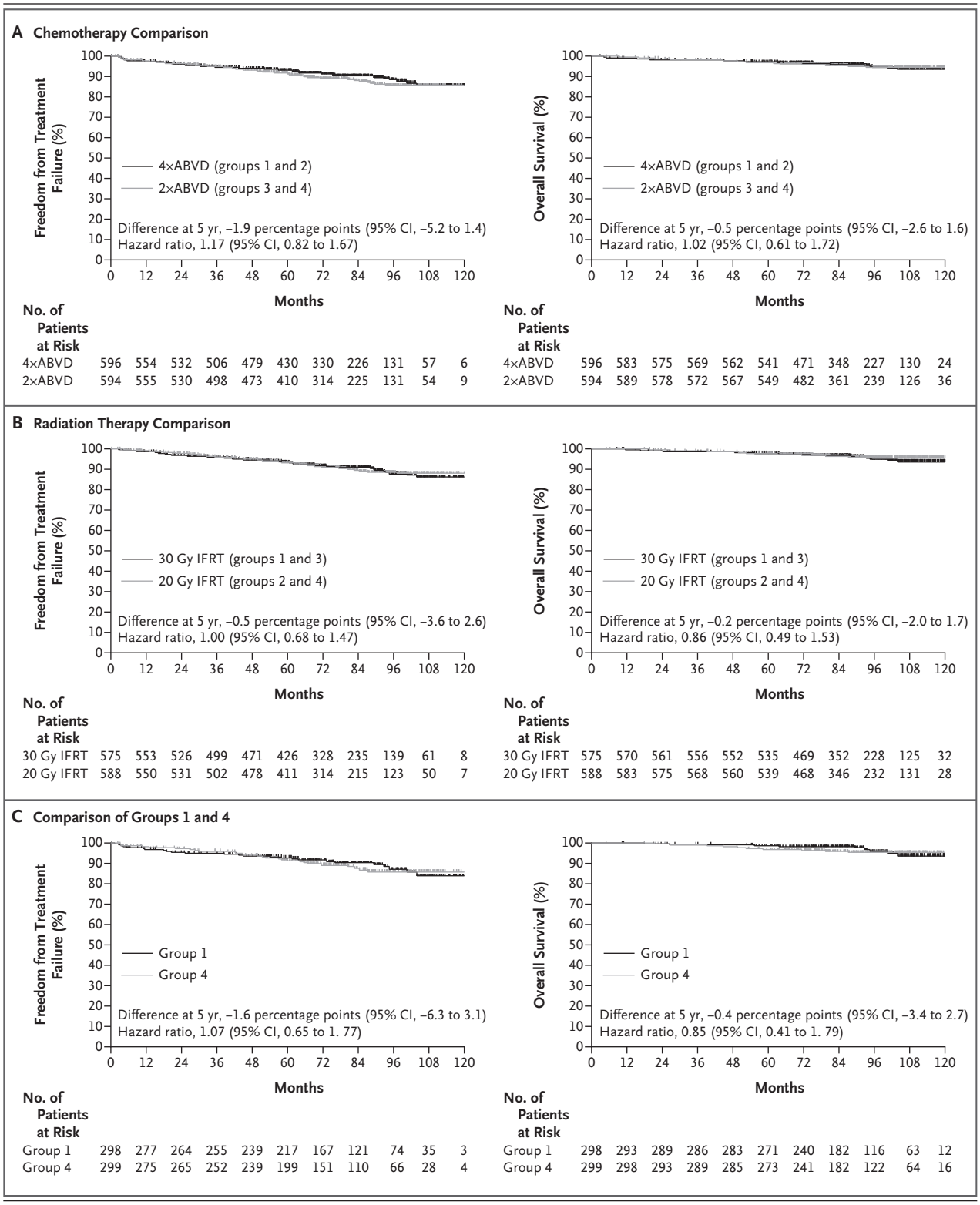
In the intention-to-treat analysis, the median observation time for the primary end point, freedom from treatment failure, was identical in the two chemotherapy groups (79 months). The rate of freedom from treatment failure at 5 years was 93.0% with four cycles of ABVD (95% CI, 90.5 to 94.8) and 91.1% with two cycles (95% CI, 88.3 to 93.2) (Table 3). On the basis of the stratified Cox regression analysis, the hazard ratio for treatment failure with two cycles of ABVD as compared with four cycles was 1.17 (95% CI, 0.82 to 1.67). The 5-year estimated group difference (two cycles vs. four cycles) was –1.9 percentage points (95% CI, –5.2 to 1.4). The sensitivity analysis, based on treatment received per protocol, showed a 5-year estimated group difference of –2.3 percentage points (95% CI, –5.6 to 2.9). On the basis of these results, the predefined 7% inferiority of two cycles of ABVD plus radiation therapy can be excluded for the primary end point, freedom from treatment failure. The intention-to-treat analysis showed no significant differences between the two chemotherapy groups for the secondary end points of overall survival (P=0.93; hazard ratio for death, 1.02 [95% CI, 0.61 to 1.72]) and progression-free survival (P=0.28; hazard ratio for progression, relapse, or death from any cause, 1.22 [95% CI, 0.85 to 1.77]).

Figure 2 (facing page). Freedom from Treatment Failure and Overall Survival.

Two pooled treatment groups were compared with respect to chemotherapy regimens (groups 1 and 2 vs. groups 3 and 4) (Panel A) and radiation therapy doses (groups 1 and 3 vs. groups 2 and 4) (Panel B). Groups 1 and 4 were also compared (Panel C). Group differences with respect to freedom from treatment failure and overall survival at 5 years were estimated on the basis of Kaplan–Meier analyses, and hazard ratios were calculated with the use of Cox regression analysis (i.e., the comparison of the chemotherapy groups was stratified according to radiation therapy group, and vice versa). (For definitions of study end points, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) Data for all patients were analyzed on the basis of the randomly assigned treatment groups (intention-to-treat principle). Data for overall survival were censored on the date when the information was last obtained; when the information lag exceeded 2 years, data on survival were obtained from registries, whenever possible. The median observation period for freedom from treatment failure was 79 months and that for overall survival was 91 months. The main analysis for the chemotherapy comparison included 1190 eligible patients who received at least 1 dose of the assigned study treatment. According to the protocol, 27 patients whose disease progressed or whose chemotherapy was discontinued before the start of radiation therapy were excluded from the main analysis for the radiation therapy comparison. (For methods and results of the sensitivity analyses, see the Supplementary Appendix.)

RADIATION THERAPY COMPARISON

In the intention-to-treat analysis of radiation therapy, the median observation time for the primary end point, freedom from treatment failure, was similar in the two groups: 77 months with 20 Gy and 80 months with 30 Gy. The rate of freedom from treatment failure at 5 years was 93.4% (95%



CI, 91.0 to 95.2) in the 30-Gy group and 92.9% (95% CI, 90.4 to 94.8) in the 20-Gy group (Table 3). The hazard ratio for treatment failure with 20 Gy as compared with 30 Gy was 1.00 (95% CI, 0.68 to 1.47). The 5-year estimated group difference (20 Gy vs. 30 Gy) was −0.5 percentage points (95% CI,

−3.6 to 2.6). The sensitivity analysis based on therapy received showed a 5-year estimated group difference of −0.2 percentage points (95% CI, −3.3 to 2.8). Thus, the predefined 7% inferiority of chemotherapy plus 20 Gy of radiation therapy can be excluded for the primary end point (freedom from treatment failure). The intention-to-treat analysis showed no significant differences between the radiation therapy groups for the secondary end points of overall survival (P=0.61; hazard ratio for death, 0.86 [95% CI, 0.49 to 1.53]) and progression-free survival (P=0.98; hazard ratio for progression, relapse, or death from any cause, 1.01 [95% CI, 0.68 to 1.48]). Overall, the rates of freedom from treatment failure might appear to be higher than those in a pure intention-to-treat analysis, since patients who dropped out before radiation therapy were excluded from this analysis. However, this was unlikely to affect between-group comparisons.

PRESPECIFIED REGRESSION ANALYSES

Prespecified factors included in the multivariate model were age above 50 years (P<0.001) and infradiaphragmatic disease (P=0.24), whereas male sex (P=0.32), systemic symptoms (P=0.75), and a low albumin level (P=0.54) were excluded. In the multivariate model including age, infradiaphragmatic involvement, and randomization group, no significant interaction was detected between the effects of the number of chemotherapy cycles and the radiation therapy dose.

COMPARISON OF GROUPS 1 AND 4

As shown in Figure 2, no significant difference in the rate of freedom from treatment failure was seen between groups 1 and 4 according to the stratified log-rank test (P=0.79). The 5-year estimate for the group difference was −1.6 percentage points (95% CI, −6.3 to 3.1), which is better than the noninferiority margin of −7 percentage points.

DISCUSSION

The aim of the HD10 study was to determine whether fewer cycles of chemotherapy and lower doses of radiation therapy could be delivered while maintaining high rates of disease control in patients with early Hodgkin's lymphoma and a favorable prognosis who were undergoing combined-approach treatment programs. No difference in efficacy was noted between the two-cycle ABVD regimen and the four-cycle regimen when each was combined with involved-field radiation therapy. This was true for the primary end point, freedom from treatment failure at 5 years, as well as for all other efficacy end points, such as response, overall survival, and progression-free survival. The results were robust with longer follow-up (8 years). No differences were seen between the intention-to-treat and the per-protocol analyses. With regard to radiation therapy, the rate of freedom from treatment failure at 5 years was 93.4% (95% CI, 91.0 to 95.2) with 30 Gy of involved-field radiation therapy and 92.9% (95% CI, 90.4 to 94.8) with 20 Gy.

The results presented here show noninferiority for both fewer cycles of chemotherapy and a lower dose of radiation, on the basis of a noninferiority margin of 7 percentage points. However, confidence intervals were rather wide for differences in freedom from treatment failure and hazard ratios. Although the 5-year estimate for the group difference between the most intensive treatment and the least intensive treatment in this study was only 1.6 percentage points, a potential difference of 6.3 percentage points in favor of the more intensive treatment cannot be excluded and must be weighed against the reductions in acute and late toxicity, lower costs of treatment, and better quality of life associated with shorter and less intense treatment.

One of the key objectives in the treatment of Hodgkin's lymphoma is to reduce the intensity of first-line therapy as much as possible while maintaining tumor control. This is most relevant for early disease with a favorable prognosis, which accounts for about 30% of all cases of Hodgkin's lymphoma,[1] since overall survival rates are compromised by late treatment-related mortality.[4-8] In the HD10 study, two cycles of ABVD as well as 20 Gy of radiation resulted in reduced rates of acute toxicity. Overall, 51.7% of patients treated with four cycles of ABVD had grade III or IV toxicity, as compared with 33.2% of those receiving two cycles (P<0.001). The rates of acute toxicity (grade III or IV) were also higher among patients treated with 30 Gy of involved-field radiation therapy than among those receiving 20 Gy (8.7% vs. 2.9%, P<0.001). Although there were numerical differences between the radiation therapy groups with respect to secondary cancers (24 [4.1%] vs. 31 [5.4%]), these findings were not significant and might have been due to chance. Clearly, longer

follow-up is needed to identify differences in long-term toxicity, such as secondary neoplasia and severe organ damage, among different treatment approaches. Given that many of the late, fatal complications of radiation therapy do not emerge until the second decade after treatment, our data cannot speak to the effect of treatment on overall survival.

Since radiation therapy is associated with the development of secondary solid tumors 5 to 25 years after initial treatment,[4-8] some groups advocate the use of chemotherapy alone for patients with early-stage Hodgkin's lymphoma. Usually, six cycles of ABVD are given, and there has been some controversy on this issue.[15-19] For this group of patients, combined-approach treatment programs have provided superior tumor control when compared directly with chemotherapy alone in some studies[20-24] but not in others.[15,19] Currently, combined-approach treatment programs are widely used as the treatment of choice in early-stage Hodgkin's lymphoma, and our study suggests that a shorter chemotherapy regimen with a lower radiation dose preserves a high level of disease control. With an overall survival rate of 95.1% at 8 years, some patients may still be overtreated.

However, the established clinical risk factors, which are based on measures such as the International Prognostic Score,[25] currently do not allow identification of patients who can be cured with even less treatment. The use of positron-emission tomography (PET) might help to discriminate between patients at low risk and those at high risk, both early in the course of chemotherapy[26] and after its completion.[27] The potential effect of PET in patients with Hodgkin's lymphoma has also been suggested in a number of retrospective, nonrandomized studies.[28-30] Several ongoing trials are evaluating the role of PET in identifying patients with early Hodgkin's lymphoma and a favorable prognosis who might not need additional radiation therapy after two cycles of ABVD (the German Hodgkin Study Group Hodgkin Disease 16 [the current GHSG HD16] trial [ClinicalTrials.gov number, NCT00736320]) or after three cycles of ABVD (the European Organization for Research and Treatment of Cancer [EORTC H10F] trial [ClinicalTrials.gov number, NCT00433433] and others).

In summary, the HD10 trial showed that in patients with early-stage Hodgkin's lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy.

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APPENDIX

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