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ORIGINAL REPORT

Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy Is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial

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ABSTRACT

Purpose
To investigate whether combined-modality treatment (CMT) with two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by extended-field radiotherapy (EF-RT) is superior to EF-RT alone in patients with early favorable Hodgkin's lymphoma (HL).

Patients and Methods
Between 1993 and 1998, 650 patients with newly diagnosed, histology-proven HL in clinical stages IA to IIB without risk factors were enrolled onto this multicenter study and randomly assigned to receive 30 Gy EF-RT plus 10 Gy to the involved field (arm A) or two cycles of ABVD followed by the same radiotherapy (arm B).

Results
At a median observation time of 87 months, there was no difference between treatment arms in terms of complete response rate (arm A, 95%; arm B, 94%) and overall survival (at 7 years: arm A, 92%; arm B, 94%; $P = .43$). However, freedom from treatment failure was significantly different, with 7-year rates of 67% in arm A (95% CI, 61% to 73%) and 88% in arm B (95% CI, 84% to 92%; $P \leq .0001$). This was due mainly to significantly more relapses after EF-RT only (arm A, 22%; arm B, 3%). No patient treated with CMT experienced relapse before year 3. Relapses were treated mainly with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, or with the combination cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD; treatment of relapse was significantly more successful in arm A than in arm B ($P = .017$). In total, there were 39 second malignancies, with 21 in arm A and 18 in arm B, respectively. The incidence was approximately 0.8% per year during years 2 to 9 and was highest in older patients ($P < .0001$) and those with "B" symptoms ($P = .012$).

Conclusion
CMT consisting of two cycles of ABVD plus EF-RT is more effective than EF-RT alone.

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INTRODUCTION

Hodgkin's lymphoma (HL) has become one of the most curable malignancies in adult oncology, with reported disease-free survival in excess of 80% at 5 years after treatment.[1,2] This success is largely due to the introduction of multiagent chemotherapy and improved radiation techniques.[3] With a large body of prospectively randomized trials performed by collaborative groups, HL is also one of the most extensively clinically evaluated malignancies. On the basis of clinical staging and risk factors, patients usually are assigned to early favorable (clinical stage [CS] I/II without risk factors), early unfavorable (CS I/II with risk factors), and advanced stages (CS III/IV, some selected IIB). Risk factors discriminating between early favorable and early unfavorable stages include large mediastinal mass, extranodal disease, high erythrocyte sedimentation rate, massive spleen involvement, and three or more areas involved.[4]

Although radiotherapy had been the mainstay of treatment for patients with early favorable HL, this has been challenged by relapse rates exceeding 30% after radiotherapy only and the risk of secondary malignancies after large-field radiotherapy.[5-7] The German Hodgkin Study Group (GHSG) thus

conducted the HD7 trial comparing extended-field radiotherapy (EF-RT) alone with two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by EF-RT in this group of patients. We report the final analysis of this trial, with a median follow-up of 87 months, proving that combined-modality treatment (CMT) is superior in terms of higher freedom from treatment failure (FFTF) and lower relapse rate when compared with EF-RT alone.

PATIENTS AND METHODS

Patients

Newly diagnosed patients with histology-proven HL in clinical stages I and II without the clinical risk factors large mediastinal mass (≥ one third of the maximum thorax diameter), extranodal disease, massive splenic involvement (diffuse infiltrations or > five focal lesions), or high erythrocyte sedimentation rate (≥ 50 mm/h in asymptomatic or ≥ 30 mm/h in symptomatic patients). Patients had to be between age 16 and 75 years, have a Karnofsky performance status more than 70%, and be previously untreated and free of concurrent disease. Patients with impaired heart, lung, liver, or kidney function, previous malignant disease, or HIV-positive status were not eligible. Minimal hematologic requirements included a WBC count more than 3,000/μL and platelet count more than 100,000/μL. Patients were also excluded from the study if they had chronic obstructive lung disease, if they were pregnant or lactating, or if they had HL as part of a composite lymphoma. Biopsy material was examined by the local pathologist and then reviewed centrally by at least one member of a panel of six HL pathology experts. All patients had to provide written informed consent before study entry.

Study Design

Patients were registered and treated in 189 hospitals and practices in Germany, Switzerland, Italy, and the Czech Republic. After clinical staging, patients were randomly assigned centrally at a ratio of 1:1 as follows: arm A, radiotherapy of 30 Gy in EF-RT technique plus 10 Gy to the involved field (IF); arm B, two cycles of ABVD followed by identical radiotherapy (Fig 1). Stratification factors included center, age (< 40 *v* ≥ 40 years), sex, supradiaphragmatic versus infradiaphragmatic involvement, and stage (CS I *v* CS II *v* pathologic stage I/II).

Chemotherapy

Patients in arm B had two cycles of ABVD applied before radiotherapy. ABVD was administered in standard doses consisting of doxorubicin 25 mg/m^2 (days 1 and 14), bleomycin 10 mg/m^2 (days 1 and 14), vinblastine 6 mg/m^2 (days 1 and 14), and dacarbazine 375 mg/m^2 (days 1 and 14). Treatment was postponed until recovery if the WBC was less than 2,500/μL or the platelet count was less than 80,000/μL on the day scheduled for re-treatment. Granulocyte colony-stimulating factor was administered if clinically indicated according to the American Society of Clinical Oncology guidelines until leukocyte recovery.[8]

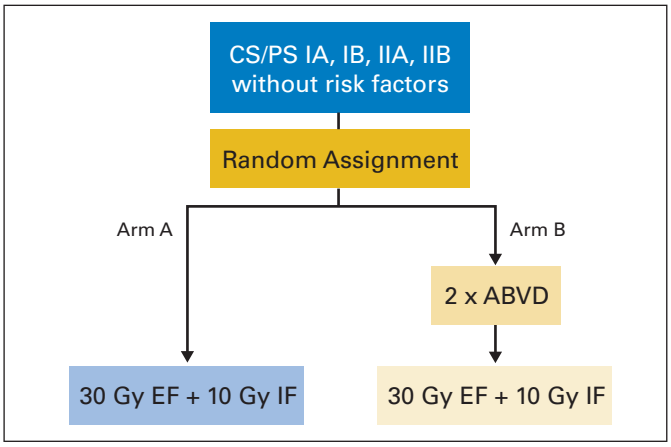

Fig 1. Design of the HD7 trial. Patients in early favorable stages without risk factors were included. Risk factors included large mediastinal mass, massive spleen involvement, extranodal involvement, high erythrocyte sedimentation rate, and three or more lymph node areas. EF, extended field, IF, involved field; ABVD, doxorubicin 25 mg/m^2 days 29 + 43, bleomycin 10 mg/m^2 days 29 + 43, vinblastine 6 mg/m^2 day 29 + 43, and dacarbazine 375 mg/m^2 day 29 + 43; CS, clinical stage; PS, pathologic stage.

Radiotherapy

Before treatment, all sites of disease were defined and documented by the treating oncologist and radiotherapist. Appropriate radiotherapy according to treatment arm was then planned centrally by the expert radiation oncology review panel. Patients received 30 Gy EF-RT (spleen, 36 Gy) followed by an additional 10 Gy to the IF. Single fraction size was 1.8 to 2.0 Gy administered five times a week. The definition of EF and IF radiotherapy as described previously was used.[4]

Evaluation of Response and Follow-Up

If no event occurred, FFTF and overall survival (OS) were each defined as the time from random assignment until the date of last information. Definitions of complete remission (CR), partial remission, no change, progressive disease, and relapse were used as described.[4] FFTF was defined as the time from random assignment to the first of the following events: progression during therapy, lack of CR at the end of protocol treatment, relapse, or death as a result of any cause.

RESULTS

Between February 1994 and March 1998, 650 patients were randomly assigned to treatment arms. A total of 23 patients (3.5%) were not qualified for this study and were excluded from additional analysis. Reasons for exclusion were wrong stage/risk factors (n = 11), review pathology diagnosis not HL (n = 8), or severe concomitant disease (n = 4). Therefore, 627 patients were included in this analysis: 311 in arm A and 316 in arm B. The primary end point could be evaluated for all of these patients. Ten patients (six in arm A and four in arm B) did not begin protocol treatment because of the patient's wish (n = 6), protocol violation (n = 2), or change in assessment of treatment required (n = 2). These patients were included in the main analyses. In addition, eight patients in arm A and 22 patients in arm B began but did not complete protocol treatment (11 terminated treatment during chemotherapy, six terminated treatment between modalities, and 13 terminated treatment during radiotherapy). All other patients received the treatment as planned.

Patient Characteristics

As shown in Table 1, patient characteristics were well balanced between the two arms. With a median age of 36 years, most patients (71%) were between 20 and 50 years old. The male-to-female ratio was 59:41. Histology review (expert panel) revealed 46% nodular sclerosis, 32% mixed cellularity, 14% lymphocyte predominant, 4% lymphocyte-rich, and 4% other HL subtypes. Forty-one percent of patients were in stage IA, 53% were in stage IIA, and 6% in total had "B" symptoms.

Toxicity and Mortality

A total of 283 patients in arm B were available for analysis of acute toxicity during ABVD therapy (Table 2). Overall, the most commonly observed toxicities were leukopenia (grade 3, 11%), hair loss (grade 3, 9.9%), and nausea (grade 3, 4.6%). There were few patients with grade IV toxicity, including leukopenia, nausea, kidney toxicity, and hair loss. A total of 532 patients were included for analysis of acute toxicity

Table 1. Patient Characteristics

Characteristic	Arm A (%; n = 311)	Arm B (%; n = 316)	Total (%; n = 627)
Age, years			
≤ 20	6	5	5
21-30	25	31	28
31-40	24	24	24
41-50	20	18	19
51-60	13	14	14
61-75	12	8	10
Median	38	34	36
Range	16-75	16-73	16-75
Sex			
Female	42	39	41
Male	58	61	59
Histology			
LP	17	10	14
LR	3	4	4
NS	43	50	46
MC	34	30	32
UC	3	4	4
Stage			
IA	41	43	42
IB	3	3	3
IIA	54	50	52
IIB	2	4	3

Abbreviations: LP, lymphocyte predominant Hodgkin's lymphoma; LR, lymphocyte rich classical Hodgkin's lymphoma; NS, nodular sclerosis; MC, mixed cellularity; UC, unclassified.

Table 2. Acute Toxicity During Chemotherapy (arm B only; WHO grades 3 and 4)

Toxicity	Grade	Arm B (%) (n = 283)
Leukopenia	3	11.0
	4	0.4
Thrombopenia	3	0.4
	4	—
Anemia	3	0.4
	4	—
Nausea	3	4.6
	4	0.4
Heart	3	0.4
	4	—
Kidney/bladder	3	—
	4	0.4
Hair loss	3	9.9
	4	0.7
Pain	3	1.1
	4	—
Nervous system	3	0.7
	4	—
Mucositis	3	0.4
	4	—

during radiotherapy (Table 3). Major toxicities (WHO grade 3) included nausea (4.3%), pharynx (2.1%), and leukopenia (1.7%), with no clinically relevant differences between treatment arms. Thus, two cycles ABVD before radiotherapy did not lead to increased acute toxicity during radiotherapy.

Causes of death during the study and in the follow-up period are listed in Table 4. A total of 51 patients died (8.1%): 28 in arm A and 23 in arm B. There were no significant differences between treatment arms, although mortality due to acute first-line or salvage toxicity was higher in the EF-RT–only arm as compared with the CMT arm (seven *v* two patients, respectively).

The total number of secondary malignancies was 39 (6.2%). There were three acute myeloid leukemias/myelodysplastic syndromes, 14 non-Hodgkin's lymphomas (NHLs), 21 solid tumors, and one chronic myeloid leukemia. The most often reported solid cancers included small-cell lung (n = 5), skin (n = 4), and breast (n = 3). Eleven of the solid tumors occurred in irradiated areas, three occurred in nonirradiated areas, and for seven tumors it was unknown or unclear (data not shown). There were no significant differences between treatment arms (Table 5). Kaplan-Meier curves for second malignancies also showed similar rates in each arm (Fig 2; $P = .52$). Between years 2 and 9, the incidence remained fairly constant at approximately 0.8% per year; numbers at risk were too small for reliable estimates (n < 50; SE ≥ 3%) beyond year 9. The incidence of second malignancy was higher in older patients ($P < .0001$) and in those with initial B symptoms ($P = .012$).

Treatment Outcome and Survival Rates

A total of 94.6% (arm A) and 93.9% (arm B) of patients achieved CR (Table 6). The median observation time for all patients was 87 months. Kaplan-Meier plots for FFTF and OS are shown in Figures 3A and 3B. At 7 years, OS was 92% in arm A (95% CI, 88% to 95%) and 94% in arm B (95% CI, 91% to 97%; $P = .43$). FFTF was 67% in arm A (95% CI, 61% to 73%) and 88% in arm B (95% CI, 84% to 92%). The difference for FFTF was significant ($P < .0001$). There were markedly more relapses after EF-RT only as compared with CMT (arm A, 21.9%; arm B, 3.2%; Table 6), and slightly more patients with progressive disease (arm A, 2.3%; arm B, 0.6%; $P = .084$). Of 78 patients who experienced relapse, 76 (97%) received chemotherapy and 11 (14%) had additional radiotherapy. Forty-five percent received bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; 24% received cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD; 19% received

Table 3. Acute Toxicity During RT (WHO grade 3 or 4)

Toxicity	Grade	Arm A, RT (%; n = 271)	Arm B, RT (%; n = 261)	Total (%; N = 532)
Leukopenia	3	2.6	0.8	1.7
	4	—	—	—
Nausea	3	3.3	5.4	4.3
	4	—	—	—
Infection	3	—	0.4	0.2
	4	—	—	—
Skin	3	—	2.7	1.3
	4	—	—	—
Pharynx	3	2.6	1.5	2.1
	4	0.4	0.4	0.4
Larynx	3	0.4	0.4	0.4
	4	—	0.4	0.2
Esophagus	3	2.2	0.8	1.5
	4	0.4	0.4	0.4

Abbreviation: RT, radiation therapy.

Table 4. Causes of Death According to Treatment Arm

Cause of Death	Arm A (n = 311) No. of Patients	Arm A (n = 311) %	Arm B (n = 316) No. of Patients	Arm B (n = 316) %	Total (N = 627) No. of Patients	Total (N = 627) %
Hodgkin's lymphoma	4	1.3	4	1.3	8	1.3
Toxicity, first-line therapy	3	1.0	1	0.3	4	0.6
Toxicity, salvage therapy	4	1.3	1	0.3	5	0.8
Second malignancy	6	1.9	6	1.9	12	1.9
Heart/circulation	5	1.6	6	1.9	11	1.8
Lung	3	1.0	2	0.6	5	0.8
Other or unknown	3	1.0	3	0.9	6	1.0
Total	28	9.0	23	7.3	51	8.1

ABVD, 6% had some other chemotherapy, and 3% had no salvage treatment; there were no significant differences between treatment arms (data not shown). The survival of these patients after relapse is shown in Figure 4. For the 68 patients experiencing a relapse after EF-RT only (arm A), survival was significantly longer than for those 10 patients experiencing a relapse after CMT (arm B; $P = .0033$). Similarly, freedom from second failure was significantly better at relapse after EF-RT alone than at relapse after CMT ($P = .017$).

Whereas initial involvement (all patients) was primarily supradiaphragmatic (a total of 1,324 involved sites, as opposed to 74 involved infradiaphragmatic sites), involvement at relapse in 78 patients was mainly infradiaphragmatic: a total of 69 involved nodal infradiaphragmatic sites were observed (24 mesenteric/para-aortic, 45 iliac/inguinal/femoral), as opposed to 42 involved nodal supradiaphragmatic sites. Thirty-one sites of relapse were extranodal. This pattern was also observed in arm B, in which there were 11 infradiaphragmatic and five supradiaphragmatic involved nodal sites. Relapse was classified as stage I in 16 patients, stage II in 13 patients, stage III in 11 patients, stage IV in 18 patients, unknown in 20 patients, asymptomatic in 36 patients, and symptomatic in 22 patients, with no significant differences between treatment arms.

Table 7 describes the FFTF events in each arm analyzed according to the type of event and the time period in which the event occurred. The number of patients failing to reach a CR under protocol therapy was similar in both arms (arm A, 12 patients; arm B, 15 patients). Relapses occurred much more frequently in arm A (n = 68), mostly within years 0 to 1 and 2 to 4, whereas in arm B (n = 10 relapses) no relapses occurred within the first 2 years. Second malignancy deaths (n = 8) occurred in years 2 to 7, although from the incidence curves in Figure 2, it is apparent that more deaths will occur in later years. Deaths from heart (n = 9) and lung (n = 3) disease were distributed over the entire observed time period. Heart-related deaths were not significantly more frequent in arm B (six *v* three).

Adherence to Radiation Fields

The radiotherapy panel reviewed the planning images of 529 patients (84%). Of these reviewed cases, 348 (66%) were assessed as

Table 5. Secondary Malignancies According to Treatment Arm

Secondary Malignancy	Arm A (n = 311) No. of Patients	Arm A (n = 311) %	Arm B (n = 316) No. of Patients	Arm B (n = 316) %	Total No. of Patients	Total %
AML/MDS	1	0.3	2	0.6	3	0.5
NHL	9	2.9	5	1.6	14	2.2
Aggressive B-NHL	5		3			
Follicular	1		2			
Others	3					
Solid tumors	11	3.5	10	3.2	21	3.3
SCLC	1		4			
Colorectal	2		1			
Breast	2		1			
Skin*	1		3			
Other†	5		1			
Other	—		1 chronic myeloid leukemia		1	0.2
Total	21		18		39	6.2

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; SCLC, small-cell lung cancer.
*Including two basaliomas in arm B.
†Including one of each of the following: cervix, bladder, liver, gallbladder, and testicular cancer in arm A and one hepatocellular cancer in arm B.

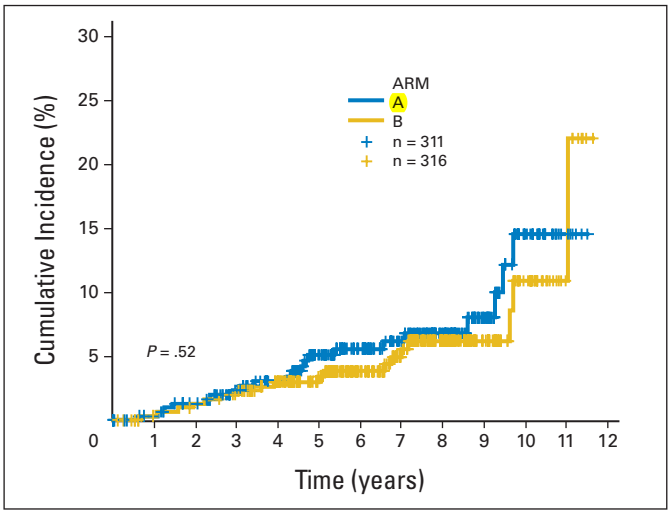

Fig 2. Incidence of second malignancies in each treatment arm using the Kaplan-Meier method. Arm A, radiotherapy only; arm B, combined-modality treatment.

showing at least one type of protocol violation (63% of arm A patients and 68% of arm B patients). Most protocol violations were classified as volume too small (44%), irradiation too protracted in time (24%), or dose too low (12%). Too little irradiation (one or more of the three aforementioned categories) was assessed in 61% of evaluated patients (arm A, 57%; arm B, 65%)—significantly more in arm B than in arm A ($P = .035$). Only 5% were assessed as showing too much irradiation (ie, volume or dose too large). FFTF did not differ significantly, as assessed using the log-rank test, between patients with and without protocol violations, either for the whole trial or for each arm separately, or between patients with and without too little irradiation, as defined above.

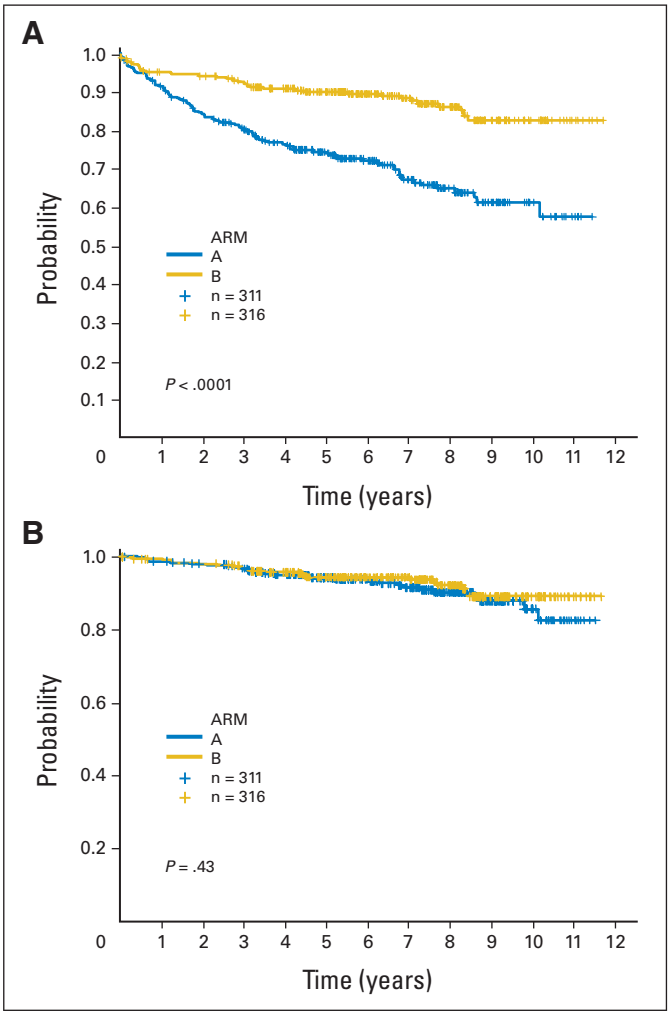

Fig 3. (A) Freedom from treatment failure comparing arm A (radiotherapy only) with arm B (combined-modality treatment). (B) Overall survival comparing arm A (radiotherapy only) with arm B (combined modality).

Table 6. Treatment Outcome, Relapse, and 7-Year Survival Rates According to Treatment Arm

Outcome	Arm A (n = 311)		Arm B (n = 316)	
	No. of Patients	%	No. of Patients	%
Treatment outcome				
Complete remission	294	94.6	297	93.9
Partial remission	—		5	1.6
No change	1	0.3	—	
Progression	7	2.3	2	0.6
Unknown	9	2.9	12	3.8
Relapse	68	21.9	10	3.2
FFTF				
At 7 years	67		88*	
95% CI	61 to 73		84 to 92	
OS				
At 7 years	92		94	
95% CI	88 to 95		91 to 97	

NOTE. Intent-to-treat analysis (n = 627 patients).
Abbreviations: FFTF, freedom from treatment failure; OS, overall survival.
*$P < .0001$.

DISCUSSION

The HD7 study reported here is the largest randomized trial reported to date comparing CMT of two cycles ABVD followed by EF-RT versus EF-RT alone in patients with early favorable HL. A total of 650 patients from 189 centers were enrolled. The following three findings emerge from this study: after CMT, there was superior FFTF (88% *v* 67%) mainly related to fewer relapses (3% *v* 22%) as compared with radiotherapy only; there was no difference in response rates and OS between treatment arms; and CMT was not associated with significantly more acute or long-term toxicity, and has emerged as the treatment of choice for this group of patients.

For decades, radiotherapy had been the standard of care for patients with early favorable HL. However, relapse rates of up to 30% prompted the evaluation of CMT as induction treatment.[1,2] In addition, CMT alleviated the need for aggressive staging procedures including laparotomy.[3] A meta-analysis based on individual data of 3,088 patients from 23 randomized trials in which CMT was compared with radiotherapy only supported the role of CMT in early favorable HL.[5] In the meta-analysis, the addition of chemotherapy to

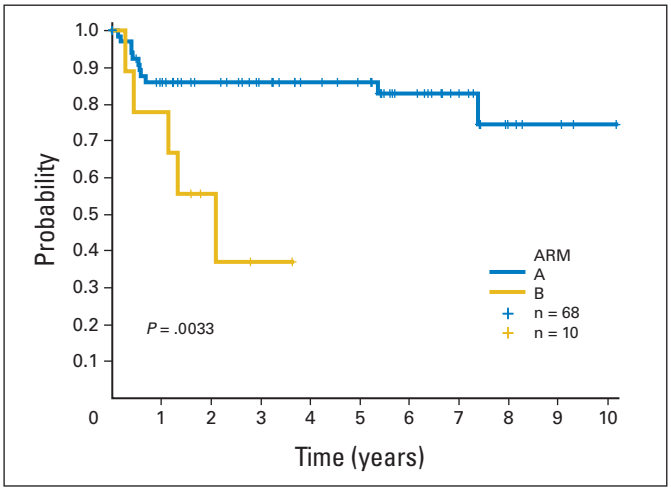

Fig 4. HD7 survival after relapse. Arm A, radiotherapy only; arm B, combined-modality treatment.

radiotherapy halved the 10-year risk of failure (15.8 *v* 32.7%; $P < .00001$) with a small, nonsignificant improvement in survival (79.4 *v* 76.5%). Most of the trials included in this analysis were conducted between 1967 and 1988 using mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) or MOPP-like regimen. The standard of care then changed, with the proof of better efficacy and less toxicity with ABVD when compared with MOPP.[9] Randomized controlled trials with ABVD or a similar regimen confirmed that CMT provides better tumor control when compared with the identical RT alone.[10-12] Because of its especially good prognosis, the subgroup of favorable early-stage patients with lymphocyte-predominant histology (LPHL) has been treated separately using IF radiotherapy alone in some study groups.[11,13,14] A subgroup analysis of the 64 LPHL patients (review histology) in the present data set showed a nonsignificant trend toward better FFTF in the CMT group (7-year FFTF, 96%) compared with the EF-RT–alone group (83%; $P = .070$). No difference in OS was observed between treatment arms ($P = .46$). Thus, these results suggest (inconclusively) that CMT improves tumor control even in the favorable LPHL subgroup. Other retrospective investigations have found no difference in outcome between radiation alone and CMT for LPHL.[13,15]

Apart from the choice of chemotherapy, the question of radiation field size and dose also has been evaluated. It appears that the smaller IF radiation when combined with effective chemotherapy produces similar results as compared with CMT using EF or subtotal lymphoid irradiation (STLI) fields.[4,16,17]

More recently, the use of CMT has been challenged by the use of chemotherapy alone in patients with early-stage HL.[18-20] However, tumor control after chemotherapy alone can be inferior when compared with CMT.[21-23] In addition, the European Organisation for Research and Treatment of Cancer (EORTC)/Groupe d'Etude des Lymphomes de l'Adulte had to close the arm with epirubicin, bleomycin, vinblastine, and prednisone (EBVP) only in their H9F trial because of too many recurrences.[24] Although they used six cycles of EBVP instead of the more effective ABVD regimen, these data taken together are strong arguments that CMT remains the treatment of choice in early-stage HL until proven otherwise.

The significant advances in the treatment of patients with localized HL have created an increasing need to reduce treatment-associated adverse effects as much as possible. In addition to acute toxicity, long-term HL cancer survivors can experience sequelae such as coronary artery disease, heart failure, pulmonary toxicity, gonadal dysfunction, fatigue, and others.[25,26] Most concern, however, has been attributed to second malignancies comprising acute leukemias, NHLs, and solid tumors.[27-29] Risk factors for the development of second malignancies include radiation dose, field size, and choice of cytostatic drug and total amount administered. In patients with early favorable HL, mortality from causes other than HL increases over time, exceeding the HL-related mortality after 12 to 15 years.[6] Thus, treatment results in patients with early favorable HL need to be counterbalanced carefully against late mortality. Importantly, the trial reported here at a median observation time of 87 months showed no difference in

Table 7. FFTF Events According to Type and Time Period

Arm	Event Type	No. of Events in Period (years) 0- < 2	2- < 5	5- < 8	8- < 12	Total
A	No CR attained	12	—	—	—	12
	Relapse	31	25	10	2	68
	Death in CR: acute toxicity	2	—	—	—	2
	Death in CR: second malignancy	—	1	2	—	3
	Death in CR: heart	—	2	—	1	3
	Death in CR: lung	—	—	1	1	2
	Death in CR: other	—	—	2	—	2
Total		45	28	15	4	92
B	No CR attained	15	—	—	—	15
	Relapse	—	5	4	1	10
	Death in CR: acute toxicity	—	—	—	—	—
	Death in CR: second malignancy	—	3	2	—	5
	Death in CR: heart	2	3	—	1	6
	Death in CR: lung	1	—	—	—	1
	Death in CR: other	—	1	—	1	2
Total		18	12	6	3	39

Abbreviations: FFTF, freedom from treatment failure; CR, complete remission.

number and type of secondary malignancies between CMT (n = 18) and EF-RT alone (n = 21). In total, there were three myeloid leukemias/myelodysplastic syndromes, 14 NHLs, 21 solid tumors, and one chronic myeloid leukemia. With the caveat that more events will occur with longer follow-up, at this time there is no increased risk of secondary malignancies after CMT as compared with EF-RT alone. Similar findings were reported from cancer registries, indicating that the cumulative risk of second malignancies more than 20 years after treatment was higher for those patients receiving EF-RT alone when compared with CMT.[30] More recently, a systematic review evaluating secondary malignancies after different treatment modalities in a total of 9,312 patients from 37 trials confirmed that CMT was superior to EF-RT alone in terms of OS (odds ratio [OR], 0.76; $P = .0004$), progression-free survival (OR, 0.49; $P < .0001$), and second malignancies (OR, 0.78; $P = .03$).[31,32] The excess in second malignancies was due mainly to solid tumors and seemed to be caused by greater need for salvage therapy after EF-RT alone.

One unexpected finding in this trial was that survival in 68 patients who experienced relapse after EF-RT alone was significantly better than for those 10 patients who experienced relapse after CMT ($P = .003$). Similarly, freedom from second treatment failure was better after EF-RT alone than after CMT ($P = .017$). We had shown before that the prognosis of patients relapsing after 4 cycles of chemotherapy is similar to those relapsing after 8 cycles of chemotherapy.[33] The data presented here suggest that even patients who experienced relapse after two cycles of ABVD followed by EF-RT seem to be more resistant to conventional chemotherapy. Given that OS in HD7 is similar in both treatment arms, one could question whether CMT is the treatment of choice in this group of patients. However, the relapse rate in patients receiving EF-RT only is much higher than in those receiving CMT. In addition, modern CMT strategies use smaller radiation fields, which might contribute to better treatment outcome at relapse.

At the time this study was initiated (February 1994), the EORTC had just closed enrollment of their H7F trial comparing six cycles of EBVP followed by IF-RT versus RT only (STLI plus spleen). This strategy produced similar OS and better EFS in the CMT-treated group in a total of 333 patients with early favorable HL. The GHSG HD7 trial presented here used what has since become the chemotherapy of choice (ABVD) but the larger EF-RT. Given that EBVP is inferior to ABVD and EF is not needed in ABVD-based CMT, the H7F trial by the EORTC and HD7 presented here redefined the standard of care for early favorable HL as two cycles of ABVD followed by IF-RT. The EORTC has confirmed the superiority of CMT in their H8F study, in which a total of 272 patients received either radiotherapy only (STLI plus spleen) or three cycles of MOPP/ABV hybrid with IF-RT.[12] Interestingly, the 4-year OS was better in the CMT-treated patients (99% *v* 95%; $P = .019$).

Most GHSG clinical trials for early-stage HL aimed at reducing toxicity: the predecessor study (HD4) had included a total of 376 pathologically staged patients and demonstrated that radiotherapy dose to the noninvolved EF can be reduced from 40 to 30 Gy without loss of efficacy.[34] The recently completed HD10/HD11 trials for patients with early HL suggest that reduction of radiation dose in the IF to 20 Gy might be possible after two to four cycles of ABVD, although the final results are still pending.[35,36] Importantly, HD10 (with a total of 1,370 randomly assigned patients) also clearly demonstrates that even when combined with IF radiotherapy, two cycles of ABVD are equally effective as four cycles. In addition to possibly defining better biologic or clinical risk factors for patients with early stage HL, the use of positron emission tomography might have an impact on future HL trials not only in the diagnostic work-up,[37] but also as an early indicator of response.[38] Thus, current plans for the next trial generation in early and advanced HL include the use of positron emission tomography as a prognostic indicator.

In summary, the randomized HD7 trial presented here shows that CMT consisting of two cycles of ABVD plus EF-RT is superior in terms of disease control and has similar toxicity compared with EF-RT alone. Thus, CMT is being regarded as standard of care for early favorable HL patients by most groups, with open questions related to the optimal radiation dose and field size.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).