VOLUME 22 · NUMBER 14 · JULY 15 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

ABVD Plus Subtotal Nodal Versus Involved-Field Radiotherapy in Early-Stage Hodgkin's Disease: Long-Term Results

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Submitted December 30, 2003; accepted April 23, 2004.

Supported in part by Associazione Italiana Ricerca sul Cancro, Milano, Italy.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2214-2835/$20.00

DOI: 10.1200/JCO.2004.12.170

ABSTRACT

Purpose
Radiation therapy (RT) alone can cure more than 80% of all patients with pathologic stage IA, IB, and IIA Hodgkin's disease, but some prognostic factors unfavorably affect treatment outcome. Combined-modality approaches improved results compared with RT, but the optimal extent of RT fields when combined with chemotherapy warranted additional evaluation.

Patients and Methods
In February 1990, we activated a prospective trial in patients with early, clinically staged Hodgkin's disease to assess efficacy and tolerability of four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by either subtotal nodal plus spleen irradiation (STNI) or involved-field radiotherapy (IFRT).

Results
Main patient characteristics were fairly well balanced between the two arms. Complete remission was achieved in 100% and in 97% of patients, respectively. The 12-year freedom from progression rates were 93% (95% CI, 83% to 100%) after ABVD and STNI, and 94% (95% CI, 88% to 100%) after ABVD and IFRT, whereas the figures for overall survival were 96% (95% CI, 91% to 100%) and 94% (95% CI, 89% to 100%), respectively. Apart from three patients who developed second malignancies in the STNI arm, treatment-related morbidities were mild.

Conclusion
Present long-term findings suggest that, after four cycles of ABVD, IFRT can achieve a worthwhile outcome. The limited size of our patient sample, however, had no adequate statistical power to test for noninferiority of IFRT versus STNI. Despite this, ABVD followed by IFRT can be considered an effective and safe modality in early Hodgkin's disease with both favorable and unfavorable presentation.

J Clin Oncol 22:2835-2841. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Long-term follow-up of laparotomy-staged patients treated with extensive subtotal nodal radiation therapy (RT) alone have reported a 10-year relapse-free survival of 75% to 85% for early stages of Hodgkin's disease.[1-3] Patients presenting with unfavorable indicators (such as bulky disease, pulmonary hilus involvement, and extranodal lesions) remain at risk of experiencing local and distant relapses despite extensive irradiation.[4-7] To decrease the risk of failure of RT treatment, a combined-modality approach with both RT and chemotherapy was proposed, particularly in patients with unfavorable prognostic factors. With this approach, approximately 90% of patients can be cured of their disease; even in less favorable settings, combined-modality therapy can achieve a relapse-free survival of approximately 75%.[8,9] Although the various combined approaches tested so far have resulted in a superior outcome compared with RT alone in terms of disease-free survival improvement, few studies could demonstrate a long-term survival advantage. In fact, patients experiencing disease relapse from RT alone could be successfully treated with salvage chemotherapy.[10-12] A major ar-

gument against the use of combined modality as first-line therapy in early-stage Hodgkin's disease seems to be an increased risk of iatrogenic morbidity and mortality relative to the use of anticancer drugs, especially alkylating agents, associated with extensive irradiation. The occurrence of iatrogenic sequelae probably could be prevented by avoiding the need of staging laparotomy and splenectomy, using less toxic but effective combination regimens to control occult sites of the disease, and reducing the doses and fields of RT.

Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy currently is considered the gold standard for Hodgkin's disease and it is associated with a significantly lower potential for leukemogenesis and gonadal toxicity.[13-16] In February 1990, we chose to use this regimen and activated a prospective study in patients with clinical stages (CS) IA, IB, and IIA disease testing four cycles of ABVD chemotherapy followed by subtotal nodal plus spleen irradiation (STNI) versus four cycles of ABVD followed by involved-field radiotherapy (IFRT). The aim of this article is to present the final results in terms of both treatment efficacy and iatrogenic sequelae.

PATIENTS AND METHODS

Patient Eligibility and Study Design

Since February 1990, consecutive patients aged between 16 and 70 years, with untreated early-stage (I unfavorable, IIA), biopsy-confirmed Hodgkin's disease were eligible for this randomized study. Eligibility assessment included medical history and physical examination; routine laboratory tests with CBC and leukocyte differential; and renal and liver function tests. Procedures to define CS included chest x-ray; chest, abdominal, and pelvic computed tomography (CT) or magnetic resonance imaging (MRI); bipedal lymphangiogram; gallium scan; and bilateral posterior iliac crest bone marrow biopsies. On completion of staging procedures, eligible patients were stratified according to CS and disease presentation (ie, CS I unfavorable, CS IIA favorable, and CS IIA unfavorable). The unfavorable group included at least one of the following characteristics: bulky disease (defined as mediastinal mass greater than one third of the thoracic diameter and/or nodal disease $>$ 10 cm), pulmonary hilus involvement, contiguous extranodal extent and, limited to stage I patients, presence of systemic symptoms (ie, fever, night sweats, or weight loss greater than 10% of baseline body weight).

Chemotherapy Treatment

The ABVD regimen was delivered according to the drug dosage and schedule previously described[13] and consisted of doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. All drugs were delivered intravenously on days 1 and 15 every 4 weeks. Doses of doxorubicin and vinblastine were to be delayed 1 week in the presence of neutropenia less than 1,000/μL and reduced by 50% in the presence of toxicity persistent for more than 1 week. No dose modifications were planned for bleomycin and dacarbazine in the presence of hematologic toxicity. Administration of hematopoietic growth factors (granulocyte colony-stimulating factor) was not routinely planned and was allowed only in the presence of repeated neutropenia or after episodes of febrile neutropenia.

RT Treatment

RT started 4 weeks after the last cycle of chemotherapy and after complete restaging was achieved. Total doses to previously involved sites ranged from 36 Gy (in patients with confirmed complete remission) to 40 Gy (in patients with unconfirmed complete remission or partial remission). In patients allocated to receive STNI, the planned dose to uninvolved sites was 30.6 Gy.

Daily fractionation, for treatments either above or below the diaphragm, was 0.90 + 0.90 Gy for 5 days per week, and was given through anteroposterior and posteroanterior equally weighted portals, usually using a 6-MV linear accelerator for the supradiaphragmatic irradiation and a 6- or 18-MV linear accelerator, depending on the thickness of the area, for the infradiaphragmatic treatments. Source-to-skin distance was 110 to 120 cm for supradiaphragmatic RT, and 120 cm or more for infradiaphragmatic RT. Portal films were obtained at the treatment unit on day 1 and during treatment. Personalized immobilization devices were used for each patient requiring supradiaphragmatic irradiation.

Target volumes were defined on the basis of postchemotherapy nodal dimensions and delineation was obtained on standard x-ray. No CT simulation or computerized treatment plans were performed. After setup was planned at a conventional simulator, personalized shields were obtained in all the patients with more than one site to be treated, using 10-cm-thick personalized blocks (corresponding to five half-value layers).

In patients allocated to received IFRT, irradiation was to be administered to all initially involved regions with one single field, whenever possible. In Hodgkin's disease limited to the neck, the upper limit of the field was 1 cm above the apex of the mastoid and the lower margin was designated above sternoclavicular joint. When the supraclavicular region was involved, the whole homolateral neck was treated. Irradiation of the mediastinum was extended to both hilar nodes, the upper limit was the top of T1 and the lower limit usually was placed at T8-9. The limits of the lung blocks were at 4 to 5 cm from the lower border of the clavicle, 1 cm inside the inner margin of the ribs, and at 1 to 2 cm laterally to the hilar regions. In patients presenting with involvement of mediastinum, neck, and axillae, mantle irradiation was planned. A two-dimensional map of the dose distribution was prepared to calculate different thickness in several points (two for neck, two for mediastinum, and one for axilla) and daily dose was calculated to be given at the midplane in the central axis. During the treatment, when the prescribed dose was reached at one or more sites, the sites were excluded from irradiation either by the use of external blocks or by the creation of a new personalized shield. The thoracic spinal cord was never shielded, whereas the irradiation to the cervical cord was blocked after 23.4 Gy, from C1 to the lower margin of C7, and in the posteroanterior field only when the planned dose to the neck was 36 Gy or higher. Subcarinal blocks for heart shielding were never used. In patients presenting with subdiaphragmatic disease, only the involved nodal regions were to be irradiated. The upper limit of the para-aortic field was tailored by leaving a gap of one vertebral body from the lower limit of the mediastinal field; the lower limit included L4. Daily dose was calculated at the midplane of the patient's thickness measured on the central axis. Personalized shields were adopted.

In patients allocated to receive STNI, mantle RT, as previously described, was started first and was followed by irradiation to the subdiaphragmatic region, which included the para-aortic

nodes and the spleen. Pelvic nodes were irradiated only if involved at diagnosis.

Toxicity Evaluation

In addition to acute adverse effects, patients were evaluated for delayed toxicity. Lung toxicity was assessed by thoracic x-ray, spirometric parameters, arterial blood gas analysis, and diffuse capacity of the lung for carbon monoxide (DLCO), and was graded according to the Radiation Therapy Oncology Group scale for pulmonary toxicity. Cardiac function was evaluated by clinical questioning and examination, ECG, and assessment of left ventricular ejection fraction (LVEF) using RBCs labeled in vivo with technetium-99 and scanning 10 minutes after injection using a gamma camera. An LVEF value more than 50% at rest was considered normal. All examinations were performed before starting ABVD and before starting RT, at 6 months after the end of treatment, and once a year during the first 3 years after completion of all therapies.

Follow-Up Evaluation and Response Assessment

All patients had a CBC before each drug administration and weekly during irradiation. Physical examination, routine laboratory tests, chest x-ray, and plain film of the abdomen to control the lymphangiogram (until residual lymphangiographic contrast was present) were repeated after every cycle of chemotherapy, 1 month from the completion of RT, every 3 months during year 1, every 4 months during years 2 and 3, and every 6 months during years 4 and 5. In patients in continuous complete clinical remission, all follow-up examinations were then repeated every 12 to 18 months.

Treatment response was assessed clinically and by repeating all CT, MRI, and gallium scans that were positive at diagnosis; these tests were performed within 4 weeks from the completion of ABVD chemotherapy and, if still positive, they were repeated 1 month from the end of RT or until normalization. Residual radiographic abnormalities, particularly in the mediastinum, were noted frequently at the conclusion of chemotherapy and RT by chest x-ray, CT, and/or MRI. In these patients, assessment of remission according to the Cotswold's criteria[17] was performed using additional findings achieved with gallium scan evaluation.

Percentage of Optimal Dose and Dose-Intensity of ABVD

The percentage of optimal dose was calculated as follows. For all patients and for each drug we calculated the total dose planned according to the protocol and the total dose actually administered. The total dose administered was then divided by the total planned dose. The percentage of optimal dose of ABVD represents the average of the four drugs given.

The rate of administration was calculated by dividing the actual number of weeks of treatment by the planned number of weeks (ie, 10 weeks from day 1 of cycle 1 to day 15 of cycle 4). Received dose-intensity was calculated by dividing the percentage of optimal drug dosage by the rate of drug treatment.

Statistical Analysis

When the study was designed at the beginning of 1990, we were aware that demonstrating a similarity in treatment outcome between a more extensive versus a less extensive irradiation would have required a large number of patients who we were unable to enroll in an adequate period of time. For this reason, we selected the mechanism of stratified randomization to allocate patients to either ABVD followed by STNI or to ABVD followed by IFRT, so that main characteristics could be fairly well balanced between the two study arms. We also devised to continue enrollment up to a total of at least 120 consecutive patients and then to report treatment results in a descriptive rather than inferential analysis.

Freedom from progression was considered as the time elapsed from the date chemotherapy was started to the first documented treatment failure, whereas event-free survival also included second malignancies and deaths unrelated to Hodgkin's disease and its treatment. Death from all causes was taken as the end point for total survival, which was also measured from the date chemotherapy was started. The patterns of freedom from progression and total survival were estimated by means of the Kaplan-Meier product limit method.[18]

Assessment of differences in respiratory test values before and after treatment and during follow-up was made by use of the *t* test for paired samples.

All data relative to the study herein reported were managed and analyzed according to the standard operating procedures of the Operations Office of the Istituto Nazionale Tumori (Milan, Italy). This analysis was carried out on data available as of October 31, 2003. Only one patient in complete clinical remission was lost to follow-up after 8 months.

RESULTS

Patient Population and Disease Extent

From February 1990 to July 1996, a total of 140 consecutive patients were entered onto this trial and 136 eligible patients are assessable after a median follow-up of 116 months (range, 1 to 157 months). Four patients were not considered eligible because of stage III and IV disease (two patients) and refusal to be treated in our institute (two patients). According the randomization, in 66 patients RT consisted of subtotal nodal plus spleen irradiation (STNI), whereas in 70 patients RT was limited to the previous involved sites only (IFRT).

Table 1 shows the main characteristics according to the two treatment groups. Overall, the majority of patients were younger than 40 years and the median age was 29 years (range, 17 to 64 years). Nodular sclerosis histology accounted for 73% and 80% of patients in the STNI versus IFRT arm, respectively. In CS I, only three (4.5%) and five (7%) patients in each group had systemic symptoms (CS IB); there were three (4.5%) and four (6%) patients in each group with CS IA unfavorable disease, respectively. The great majority of patients had CS IIA with a favorable presentation (59% and 60%, respectively). The supradiaphragmatic presentation was the rule; in fact, subdiaphragmatic disease was documented in only two patients in each treatment group (3% and 3%, respectively). Extranodal sites of disease included lung, pleura, and pericardium.

Complete Remission

All of the 66 patients allocated to extensive irradiation received STNI as planned and achieved complete remission at the end of the combined-modality treatment; the rate of complete remission was 91% after ABVD alone. One of the 70 patients allocated to ABVD followed by IFRT died as a result of a myocardial infarction during the second ABVD

Table 1. Main Pretreatment Characteristics

Characteristic	ABVD Followed by STNI		ABVD Followed by IFRT	
	No. of Patients	%	No. of Patients	%
Total	66	100	70	100
Sex				
Male	29	44	30	43
Female	37	56	40	57
Age, years				
≤ 40	53	80	61	87
> 40	13	20	9	13
Stage				
I	6	9	9	13
II, favorable	39	59	42	60
II, unfavorable	21	32	19	27
NS histology	48	73	56	80
> 3 involved sites	12	18	12	17
Extranodal disease	8	12	6	9
Bulky disease*	13	20	15	21

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; STNI, subtotal nodal plus spleen irradiation radiotherapy; IFRT, involved-field radiotherapy; NS, nodular sclerosis.
*Mediastinal mass greater than one third of the thoracic diameter and/or nodal disease > 10 cm.

Table 2. Main Results at 12 Years

Result	%	95% CI
Freedom from progression		
Total	93	88 to 99
ABVD → STNI	93	83 to 100
ABVD → IFRT	94	88 to 100
Males	87	73 to 100
Females	97	94 to 100
Age ≤ 40 years	95	91 to 99
Age > 40 years	83	61 to 100
Stage I	93	81 to 100
Stage II, favorable	95	90 to 100
Stage II, unfavorable	88	74 to 100
Event-free survival		
Total	89	83 to 97
ABVD → STNI	87	85 to 98
ABVD → IFRT	91	85 to 98
Overall survival		
Total	95	91 to 99
ABVD → STNI	96	91 to 100
ABVD → IFRT	94	89 to 100

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; STNI, subtotal nodal plus spleen irradiation radiotherapy; IFRT, involved-field radiotherapy.

cycle and the autopsy revealed a complete disappearance of all sites of the lymphoma. All other patients received IFRT as planned and the rate of complete remission after combined-modality treatment was 97%, 86% of which were documented after ABVD alone. One patient achieved a partial response during ABVD, but showed disease progression while receiving RT. A second patient was classified as a partial responder at the end of combined therapy, but normalization of all radiologic signs was documented during the follow-up.

Overall, ABVD alone was able to achieve clinical complete remission in 89% of the patients; in one third of the patients, complete remission was documented within the third cycle.

Long-Term Treatment Outcome

Ninety-three percent of the patients allocated to receive ABVD followed by STNI and 94% of those allocated to ABVD followed by IFRT are continuously free of disease as of last follow-up (Table 2 and Fig 1). In the ABVD followed by STNI group, three patients experienced disease relapse at 18, 38, and 130 months, respectively, from the start of treatment. All three patients presented with new disease manifestations in or around previously irradiated but uninvolved sites, and two of them also had new disease sites below the diaphragm. In the ABVD followed by IFRT arm, one patient presented lymphoma progression during irradiation; disease relapse was documented in three patients at 21, 23, and 28 months, respectively, from the start of ABVD treatment. Two of the complete responders presented with both previously involved and uninvolved sites, whereas the last patient had new disease manifestations below the diaphragm.

Table 2 shows freedom from progression related to the two treatment groups and to patient characteristics and disease presentation.

As shown in Figure 2, a total of six patients have died within 12 years from starting treatment (four in the group given limited irradiation and two in the group given exten-

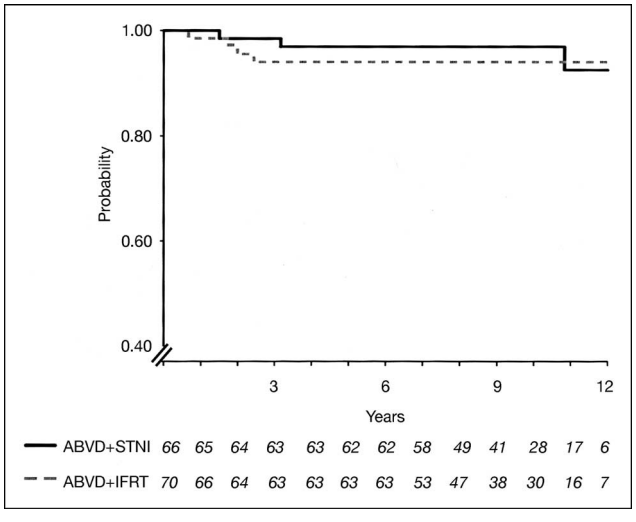

Fig 1. Freedom from progression. The number of patients at risk at yearly intervals is shown in italics. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; STNI, subtotal nodal irradiation; IFRT, involved-field radiotherapy.

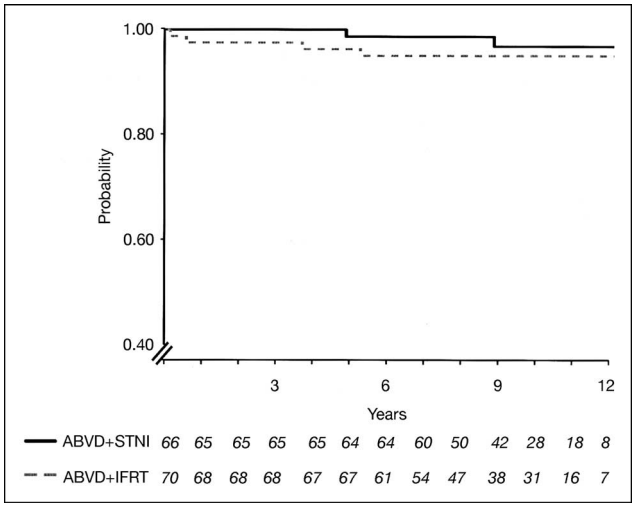

Fig 2. Overall survival. The number of patients at risk at yearly intervals is shown in italics. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; STNI, subtotal nodal irradiation; IFRT, involved-field radiotherapy.

sive RT), for a total survival rate of 94% and 96%, respectively. In the IFRT arm, two patients died as a result of lymphoma progression and one patient died as a result of myocardial infarction during the second ABVD cycle; the remaining patient died as a result of fatal hepatitis. In the STNI arm, one patient died as a result of lymphoma progression and the other patient died as a result of acute leukemia while in complete remission.

Second Malignancies

Three patients in the STNI arm (4.5%) developed second malignancies while in complete remission. One patient developed acute leukemia 18 months from the start of ABVD and died 39 months later. The other two patients presented sigmoid adenocarcinoma (22 months after the start of chemotherapy) and breast cancer (105 months after the start of ABVD) and at present are alive and in complete remission.

Treatment Compliance and Acute Toxicity

Treatment compliance during chemotherapy was good, and no patient refused to complete the combined program. Nausea and vomiting were mild because of premedication with antiemetic drugs; stomatitis occurred in 16% of the patients. Neutropenia was the most common hematologic toxicity, with grade 3 in 9% and grade 4 in 0.9% of the ABVD cycles. Grade 3 or 4 thrombocytopenia was never recorded. None of the patients required supportive therapy with hematopoietic growth factors. Infectious episodes occurred in 11% of the patients. In particular, two patients presented with positive markers for hepatitis at diagnosis and developed acute hepatitis during chemotherapy, which was reversible in one patient but rapidly progressed and was fatal in the other patient. The average percentage of ABVD doses administered was 99% (range, 79% to 109%). The median received dose-intensity was 0.84 (range, 0.57 to 1.08).

Weekly assessments of blood cell counts performed during irradiation showed that acute toxicity was mild and no treatment interruptions were required.

Median duration of the combined treatment was 7 months (range, 6 to 9 months) for patients enrolled in the STNI arm, whereas it was 6 months (range, 5 to 9 months) for the patients enrolled in the IFRT arm.

Cardiac and Pulmonary Toxicity

Before patients started ABVD, mean LVEF was 62% (range, 45% to 78%). After the combined-treatment program and after a median follow-up of 58 months, mean values were 60% (range, 45% to 73%) and 58.5% (range, 40% to 76%), respectively. LVEF below normal values was recorded in one patient after combined treatment, but the patient was asymptomatic. Among 123 patients with normal ECG findings at the start of ABVD, 13 (11%) presented with transient abnormalities during the follow-up period. In addition to the patient who developed acute myocardial infarction after the second cycle of ABVD, one patient presented a myocardial infarction at the age of 45 years (4 years after starting chemotherapy) and at present, he is alive 8 years later.

Respiratory function parameters were assessed before therapy, and repeated after completion of irradiation and after a median follow-up of 42 months (range, 21 to 61 months) from the end of all therapies (Table 3). Radiotherapy to the mediastinum was delivered in a total of 86% of the patients assessed for pulmonary toxicity. The time course of spirometric parameters and DLCO showed a significant decrease between baseline values and post-treatment values ($P < .001$), but at the last follow-up examination significant differences from baseline were detected only for total lung capacity ($P = .03$) or DLCO ($P = .004$); these tests are indicative of a subclinical restrictive syndrome. Asymptomatic decline in DLCO $\geq$ 20% from baseline values was recorded in 13 patients (18.8%) allocated to IFRT and in 17 patients (25.7%) allocated to STNI. This decline was documented in 29 of the patients at the end of irradiation, whereas in the remaining two patients it was recorded during the follow-up. Recovery was documented in the vast majority of patients during subsequent examinations, but a decline of approximately 20% from baseline values persisted unchanged after 3 years in six patients who remained asymptomatic.

Fourteen patients (seven in each treatment group) had pulmonary symptoms; 10 developed dry cough and four had mild dyspnea on exertion. Two patients were treated with low doses of corticosteroids and none of the patients developed chronic symptomatic pulmonary disease. Radiologic findings of interstitial fibrosis were present in 19 patients and were grade 1 (slight radiographic appearances) in

Table 3. Mean Respiratory Values at Baseline, Post-Treatment, and Follow-Up Examinations

	VC		TLC		RV		FEV		FEF		DLCO	
Value	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	105.9	16.5	105.2	15.3	101.7	31.3	104.8	11.5	99.0	19.7	97.4	18.6
Post-treatment	96.0	18.7	94.3	14.8	90.6	24.2	95.4	19.0	91.1	26.8	86.1	17.0
Difference*	9.8	14.8	10.3	13.0	10.4	29.4	9.4	16.6	7.8	25.0	11.3	17.8
*P**	.0001		.0001		.023		.0005		.044		.0001	
Follow-up	103.7	14.5	101.1	10.4	94.4	16.5	102.8	13.1	95.7	21.6	87.5	10.3
Difference†	2.7	12.7	4.7	13.5	7.5	36.2	2.2	12.4	3.3	21.9	8.8	18.2
P†	.18		.03		.19		.27		.34		.004	

Abbreviations: VC, vital capacity; TLC, total lung capacity; RV, respiratory volume; FEV, forced expiratory volume; FEF, forced expiratory flow; DLCO, diffuse capacity of the lung for carbon monoxide; SD, standard deviation.
*Baseline versus post-treatment.
†Baseline versus follow-up.

10 patients and grade 2 (patchy radiographic appearances) in nine patients.

Gonadal Toxicity

Seventy women were premenopausal at the time of diagnosis and only one became amenorrheic after treatment. Nineteen women became pregnant and 22 births of healthy children have been documented at the present follow-up. Thirty-five male patients consented to have a semen analysis after therapy and persistent azoospermia was documented in two patients (6%). Eight men have fathered nine normal children.

DISCUSSION

In the early 1990s, when this study was designed and activated, conventional treatment for patients with early-stage Hodgkin's disease still consisted of laparotomy and extensive irradiation to include the mantle field and para-aortic area.[19] The fairly high rate of disease recurrence after this treatment modality, especially in patients with unfavorable prognostic features, prompted some investigators to assess the effectiveness of chemotherapy or combined chemoradiotherapy in this subset of patients.[20] Despite a significantly improved disease-free survival, no apparent effects could be demonstrated on overall survival because recurrence after RT alone could be cured by salvage chemotherapy.

As patients began to survive longer after the successful treatment of Hodgkin's disease, other problems were documented in these patients at a greater frequency than one would expect in an age-matched population. Apart from late sepsis in splenectomized patients who also could suffer from complications of abdominal surgery, other major problems associated with RT and specific drug therapy were second malignancies, heart and lung disease, and sterility.[22-24] In an attempt to avoid (or at least decrease) the occurrence of these sequelae, less extensive irradiation was proposed and the well-known mechlorethamine, vincristine, procarbazine, and prednisone regimen was replaced by less toxic and potentially nonleukemogenic combinations.[20]

In contrast to the results reported in the meta-analysis published by Specht et al,[9] in which less extensive RT was associated to a higher risk of recurrence (43%) than more extensive irradiation (31%), in our case series the risks of recurrence were 6% (95% CI, 0% to 12%) after four cycles of ABVD followed by IFRT and 7% (95% CI, 0% to 17%) after four cycles of ABVD followed by STNI.

Our treatment results compare favorably with other reported series. In fact, patients with stage I to II disease treated with the Stanford V regimen (vinblastine, doxorubicin, vincristine, bleomycin, nitrogen mustard, etoposide, and prednisone) could achieve a 5-year freedom from progression of approximately 97% at the expense of minimal late toxicity.[24] However, in contrast with the Stanford V regimen, none of the patients treated with ABVD and irradiation required either hospitalization or supportive therapy with granulocyte colony-stimulating factor. In the large case series of patients with early-stage unfavorable Hodgkin's disease treated in the German Hodgkin's lymphoma study,[25] 5-year freedom from treatment failure (98.5% *v* 97.2%) and overall survival (90.8% *v* 92.4%) revealed no difference after four courses of cyclophosphamide, vincristine, procarbazine, and prednisone + ABVD followed respectively by extended-field RT or IFRT. In the German study, however, the 5-year incidence of second malignancies was 2.8% after IFRT, whereas we failed to observe any occurrence of second tumors after ABVD followed by IFRT at a median period of observation as long as 9.7 years. Finally, an abstract format the Canadian Study Group[26] reported that in early-stage disease, two cycles of ABVD and irradiation had superior 5-year therapeutic results (93%) compared with single-modality ABVD (87%). Additional details and a longer follow-up are required to assess the true therapeutic ratio of the two treatment modalities.

In our study, iatrogenic sequelae other than second malignancies also were rare. Apart from the patient who died because of an acute myocardial infarction after the second cycle of ABVD, one other patient presented infarction during the follow-up, whereas decreases in LVEF were transient and asymptomatic. Similarly, pulmonary late toxicity was low; the vast majority of patients were asymptomatic or presented mild symptoms of grade 1 to 2 lung fibrosis. Abnormalities in respiratory function tests were mainly transient and only DLCO and total lung capacity (ie, tests showing a minor restrictive disease) continued to be abnormal during the follow-up in a minority of patients who, however, remained asymptomatic.

Present long-term findings suggest that after four cycles of ABVD, IFRT can achieve a worthwhile outcome. The limited size of our patient sample, however, had no adequate statistical power to test for noninferiority of IFRT versus STNI. Despite this, ABVD followed by IFRT can be considered an effective and safe modality in early Hodgkin's disease with both favorable and unfavorable presentation.

Acknowledgment

We thank all of the patients who participated in our clinical trial. We also thank Armando Santoro, Marcello Zanini, Fulvia Soncini, and Lilli Devizzi for their invaluable advice during the planning and the conduct of the study, and Mrs. Annabella Di Florio for data management.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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