Long-term Events in Adult Patients with Clinical Stage IA-IIA Nonbulky Hodgkin's Lymphoma Treated with Four Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Adjuvant Radiotherapy: A Single-Institution 15-Year Follow-up

Ercole Brusamolino,[1] Ambrogia Baio,[2] Ester Orlandi,[1] Luca Arcaini,[1] Francesco Passamonti,[1] Vassiliki Griva,[1] William Casagrande,[2] Cristiana Pascutto,[1] Pietro Franchini,[2] and Mario Lazzarino[1]

Abstract

Purpose: To report on long-term events after short doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy and adjuvant radiotherapy in favorable early-stage Hodgkin's lymphoma.

Experimental Design: We monitored late events and causes of death over 15 years (median follow-up, 120 months) in 120 patients with nonbulky stage IA-IIA Hodgkin's lymphoma, treated with four cycles of ABVD and limited radiotherapy. Pulmonary and cardiac function tests were done throughout the follow-up. Outcome measures included cause-specific mortality, standardized mortality ratio, and standardized incidence ratio for secondary neoplasia.

Results: Projected 15-year event-free and overall survival were 78% and 86%, and tumor mortality was 3%. Standardized mortality ratio was significantly higher than 1 for both males (2.8; $P = 0.029$) and females (9.4; $P = 0.003$). The risk of cardiovascular events at 5 and 12 years was 5.5% and 14%, with a median latent time of 67 months (range: 23-179 months) from the end of radiotherapy. Pulmonary toxicity developed in 8% of patients; all had received mediastinal irradiation and the median time from radiotherapy to pulmonary sequelae was 76 weeks (range: 50-123 weeks). The risk of secondary neoplasia at 5 and 12 years was 4% and 8%, respectively, with no cases of leukemia. Fertility was preserved.

Conclusions: Long-term events were mostly related to radiotherapy; the role of short ABVD chemotherapy was very limited, as documented by fertility preservation and lack of secondary myelodysplasia/leukemia. A proportion of patients died from causes unrelated to disease progression and the excess mortality risk was mostly due to the occurrence of secondary neoplasms and cardiovascular diseases. A moderate dose reduction of radiotherapy from 40-44 Gy to 30-36 Gy did not decrease the risk of late complications; abolishing radiotherapy in nonbulky early-stage Hodgkin's lymphoma is being evaluated.

In early-stage Hodgkin's lymphoma, the combined modality therapy reduces the risk of relapse compared with radiotherapy alone and is considered, to date, the standard therapy, particularly in clinically staged patients and/or in those with unfavorable prognostic factors (1–6). Attempts have been made in the last 15 years to possibly reduce the risk of therapy-related long-term toxicity, particularly in the more favorable patient categories. Briefly, laparotomy was abolished, the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen, which had proved to be associated with a lower risk of gonadal damage (7) and secondary leukemia (8, 9), was adopted instead of regimens containing alkylating agents and procarbazine, and the dose and extension of radiotherapy were limited. Furthermore, because of the potential cardiac toxicity of doxorubicin and pulmonary toxicity of bleomycin (particularly when adjuvant mediastinal radiotherapy is given), the cumulative dose of both these drugs has been reduced by administering a limited number of ABVD courses (two to four). The results reported thus far, using brief ABVD followed by adjuvant irradiation for clinical stage IA-IIA nonbulky Hodgkin's lymphoma in adult patients (5, 10–12), have proved this approach to be highly effective at eradicating limited-stage disease, with very rare relapses and deaths from Hodgkin's lymphoma (13).

In 1990, we started a combined modality program of brief chemotherapy with four cycles of ABVD followed by adjuvant radiotherapy in adult patients with clinical stage IA-IIA Hodgkin's lymphoma. Patients with unfavorable risk factors such as systemic symptoms and/or bulky disease were excluded

Authors' Affiliations: [1]Clinica Ematologica and [2]Servizio di Radioterapia Oncologica, Istituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo, University of Pavia, Pavia, Italy

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Requests for reprints: Ercole Brusamolino, Clinica Ematologica, Istituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo, University of Pavia, Piazzale Golgi 2, 27100 Pavia, Italy. Phone: 39-0382-503-074; Mobile phone: 39-348-3520-337; E-mail: ebrusa@smatteo.pv.it.

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from this program. As to radiotherapy, we used the extended-field radiotherapy until 1997, and the involved-field radiotherapy thereafter, when data became available on the risk of secondary neoplasia after extensive radiotherapy, with particular emphasis on breast cancer after mantle irradiation in young women (14). We concomitantly reduced the cumulative irradiation dose per field (from 40-44 to 30-36 Gy) when the German Hodgkin's Study Group data indicated that dose could safely be reduced in a combined modality approach (15).

In this article, we report the mature results of this program in terms of efficacy and toxicity. We have conducted a comprehensive monitoring for late events and causes of death over a 15-year time period, with special emphasis on risk of secondary neoplasia and cardiovascular diseases.

Patients and Methods

Patient eligibility and treatment outline. This study includes 120 consecutive prior untreated patients with a diagnosis of Hodgkin's lymphoma in early clinical stage. Eligibility criteria included patients with stage IA or IIA according to the Ann Arbor criteria, with no bulky disease and systemic symptoms. Patients older than 65 years, and/or with comorbidities (cardiac, pulmonary, metabolic or neurologic diseases), or with a prior neoplasia were excluded from this study. Clinical staging procedures were done according to the Ann Arbor criteria integrated at the Cotswolds meeting. Pretreatment evaluation consisted of a complete history and physical examination, routine laboratory tests with hemogram, lactate dehydrogenase and β2-microglobulin, liver and renal function tests, chest X-rays, and chest and abdominal computerized tomography. Unilateral bone marrow biopsy was done in all cases whereas laparotomy with splenectomy was carried out only in four patients with subdiaphragmatic disease. The treatment program consisted of four cycles of chemotherapy with the ABVD regimen, followed by adjuvant radiotherapy. This program was started in 1990 and terminated in June 2003, with a median follow-up for the entire cohort of 120 months and a range from 30 to 190 months.

ABVD chemotherapy. The ABVD regimen consisted of 25 mg/m^2 doxorubicin, 10 mg/m^2 bleomycin, 6 mg/m^2 vinblastine, and 375 mg/m^2 dacarbazine, i.v., on days 1 and 15, every 28 days, for four courses. Two additional courses of ABVD were administered to patients showing a partial remission at the evaluation after the fourth course of ABVD. The granulocyte colony-stimulating factor was administered only in 12 (10%) patients who developed repeated severe neutropenia (absolute neutrophil count $<1 \times 10^9$/L) necessitating treatment delay or during episodes of febrile neutropenia.

Adjuvant radiotherapy. Radiation therapy was delivered through a megavoltage linear accelerator within 30 to 45 days after the last cycle of ABVD. Daily fractionation amounted to 1.8 to 2 Gy per day for 5 days per week, with lung, heart, and spinal marrow protection. Computed tomography simulation or computerized treatment plans were done; subcarinal blocks for heart shielding were used. Table 1 illustrates the radiation fields, the median dose administered per field, and the dose range. In the original radiotherapy program, designed in 1990, mantle irradiation was planned for patients with supradiafragmatic disease and inverted Y + mediastinal irradiation for patients with subdiaphragmatic disease. Altogether, 23% of patients in this series were given extended-field irradiation (mantle in 18%, inverted Y + mediastinal irradiation in 5%), with doses from 40 to 44 Gy. After 1997, involved-field irradiation was adopted, and the total dose per field varied from 30 to 36 Gy. As a result, 44% of patients received an involved-field radiotherapy on mediastinum and neck (median dose, 36 Gy) and 33% an involved-field radiotherapy without mediastinal irradiation (median dose, 36 Gy).

Response evaluation and follow-up. A complete response was defined by the complete regression of all measurable lesions and by the disappearance of all subjective and objective evidence of disease.

Table 1. Radiation fields and median dose per field

Radiation fields	No. patients (%)	Median RT dose (range), Gy
Mantle	22 (18)	40 (36-44)
Mediastinum and neck	53 (44)	36 (24-40)
Cervical and supraclavicular region	20 (17)	36 (30-42)
Cervical, supraclavicular region and axilla	7 (6)	36 (30-38)
Axilla alone	6 (5)	36 (34-44)
Inverted Y and mediastinum	6 (5)	40 (36-44)
Inguinal region	6 (5)	36 (30-38)
Total	120 (100)	36 (24-44)

Patients were considered to be in partial remission if they did not meet the criteria for complete response, and there was at least a 75% decrease in the sum of the products of the diameters of measurable lesions. Patients were considered to have failed to achieve a major response if initial lesions increased or failed to decrease in size. Restaging procedures were done at the end of chemotherapy and after the completion of adjuvant radiotherapy. These procedures included complete blood count, biochemistry, and lung and abdomen computed tomography imaging. Nuclear magnetic resonance was used only in special circumstances. All patients were regularly followed up every 3 months for the first 2 years after complete response, and annually thereafter. Thoracic and abdominal computerized tomography were done every 6 months for the first 2 years of follow-up, and then at the treating physician's discretion.

Late toxicity evaluation. Pulmonary function tests including spirometric evaluation of forced vital capacity and forced expiratory volume, measurement of single-breath carbon monoxide diffusing capacity, and arterial blood gas determination were done in all patients with respiratory symptoms during or after the end of therapy. Cardiac function was evaluated by two-dimensional echography and measurement of left ventricular ejection fraction; a thorough cardiac evaluation was carried out in the presence of cardiac symptoms. Thyroid hormones were tested every 6 months for the first 5 years after the end of therapy. In women, the gonadal function was assessed by menses evaluation and by testing plasma level of estradiol, progesterone, and prolactin before and after therapy. Potentially fertile women were given during chemotherapy an estrogen-progesterone combination or a gonadotropin-releasing hormone analogue for ovarian protection.

Statistical analysis of the outcome. Statistical analysis was carried out on data available as of December 31, 2005. Outcome measures included event-free, disease-free, and overall survival calculated using the product-limit method of Kaplan-Meier. Events were defined as disease progression or relapse or death resulting from any cause without disease progression. Disease-free survival included patients who achieved complete response at the end of treatment and was calculated from the time of response documentation. Overall survival was calculated from the date of diagnosis to the last follow-up or death; death from all causes was taken as the end point for overall survival. In addition, a cause-specific survival curve was calculated, considering as events only deaths from Hodgkin's lymphoma. A standardized mortality ratio was calculated to compare mortality in this series with mortality of the general population in Italy. Standardized mortality ratio is the ratio between the number of deaths observed and the number of deaths expected in the study group according to a set of reference mortality rates. A standardized mortality ratio higher than 1 indicates a mortality rate higher than that expected in the general population. Standardized mortality ratio values were tested by means of the score test; $P < 0.05$ indicates that standardized mortality ratio is significantly different from 1. The Italian population mortality rates by age, sex, and calendar year were provided by the Italian Institute of

Statistics. The actuarial risk of secondary neoplasms and cardiovascular complications was calculated using the product-limit method of Kaplan-Meier. A standardized incidence ratio for secondary neoplasia was computed as for standardized mortality ratio; the reference sex- and age-specific incidence rates were indicated by the Varese Cancer Registry for the period 1993 to 1997. The standardized incidence ratio allowed an age- and sex-adjusted comparison between the incidence of secondary neoplasms in the study cohort and the cancer incidence in a reference population.

We obtained the permission by the institutional review board to analyze the patients' clinical records for the analysis of outcome and actuarial risk of late events (observational study).

Results

Patient characteristics. The main characteristics of the study population are illustrated in Table 2. The median age was 31 years (range, 15-65 years). The most frequent histology was nodular sclerosis (69%); lymphocyte predominance and mixed cellularity accounted for 13% and 16% of total patients, respectively. Most patients were in clinical stage II (80%). Mediastinal enlargement was present in 79 (66%) patients; in 19 (24%) of them, mediastinal dimensions were borderline for bulky disease. Subdiaphragmatic disease accounted for 5% of all cases.

Response to therapy, long-term survival, and causes of death. Altogether, 118 patients were evaluated at the end of chemotherapy; 109 patients received the planned four courses of ABVD, whereas 9 patients, in unproved complete response or in partial remission at the cycle 4 evaluation, were given two additional courses of ABVD. A complete response after ABVD was documented in 110 of 118 (93%) patients. At the end of the combined modality program, a complete response was documented in 118 of 120 (98%) patients. Only two patients were refractory to therapy and eventually entered a salvage high-dose chemotherapy program followed by peripheral blood progenitor cells infusion; one of them obtained a sustained complete remission. Within a median follow-up of 120 months (range: 30-190 months), 11 of 118 (9%) remitters did relapse; the actuarial disease-free survival curve is illustrated in Fig. 1, with a projected 15-year disease-free survival of 90%. All relapses involved nonirradiated nodal sites; in three of them, extranodal sites were involved, as well. Events (relapse, progression, or death unrelated to disease progression) were registered in 21 (17%) patients; the actuarial event-free survival curve is illustrated in Fig. 2, with a projected 15-year event-free survival of 78%. Eleven (9%) patients died; the actuarial overall survival curve is illustrated in Fig. 3, with a projected 15-year overall survival of 86%. The causes of death consisted of Hodgkin's lymphoma progression in three patients, fatal secondary neoplasms in four cases (36% of all deaths), cardiovascular complications in two cases, and events unrelated to the primary disease in two cases (one suicide and one road accident). The cause-specific actuarial survival considering only deaths from Hodgkin's lymphoma progression is 97% (Fig. 3).

Table 2. Patient characteristics

Characteristics	No. patients (%)
Total	120
Men	53 (44)
Women	67 (56)
Age (y)	
Median	31
Range	15-65
<20	14 (12)
20-40	83 (69)
>40	23 (19)
Histology	
Lymphocyte predominance	15 (13)
Nodular sclerosis	83 (69)
Mixed cellularity	19 (16)
Not classified	3 (2)
Stage	
I	24 (20)
II	96 (80)
Mediastinal enlargement	79 (66)
Subdiaphragmatic disease	6 (5)
Laparotomy with splenectomy	4 (3)
Erythrocyte sedimentation rate >50 mm	18 of 83 (22)

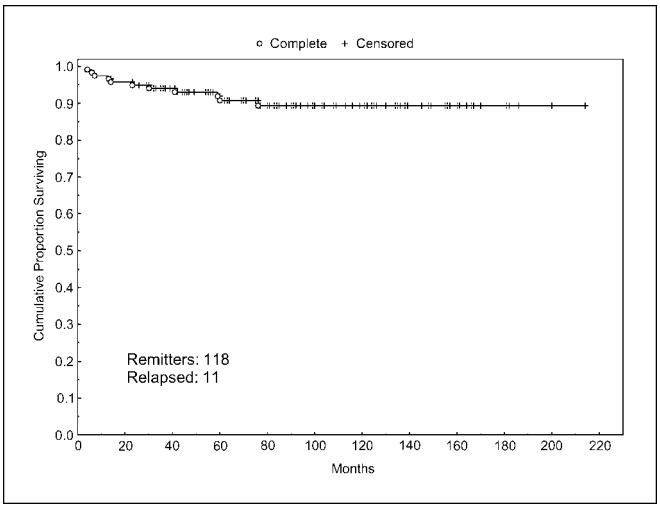

Fig. 1. Disease-free survival.

Pulmonary events. Overall, 9 (8%) patients developed signs of pulmonary toxicity; the median age of these patients at the diagnosis of Hodgkin's lymphoma was 29 years. Table 3 illustrates the main clinical features, with emphasis on acute respiratory symptoms, time to the complication, therapy received, and late pulmonary sequelae. Early acute respiratory symptoms (cough with or without exertional dyspnea) developed in five patients within variable intervals of time after the end of radiotherapy (range: 2-12 weeks); radiographic findings of interstitial pulmonary infiltrates and/or acute mediastinitis were documented in concomitance with acute respiratory symptoms. In all but one patient, acute symptoms subsided within few weeks, with no apparent impairment of the performance status. Late radiological signs consisted of aymptomatic mediastinal fibrosis in six patients and lung fibrosis with symptomatic restrictive syndrome in three patients. Pulmonary function tests showed a >15% reduction of the forced expiratory volume in all three cases, with a marked reduction of carbon monoxide diffusing capacity in one case. All patients developing pulmonary symptoms (early or late) had received mediastinal irradiation (median dose, 40 Gy; range: 36-44 Gy) and a median cumulative dose of bleomycin of 80 mg/m^2 (range: 60-100 mg/m^2). The median interval from the end of radiotherapy to late pulmonary sequelae was 76 weeks (range: 50-123 weeks).

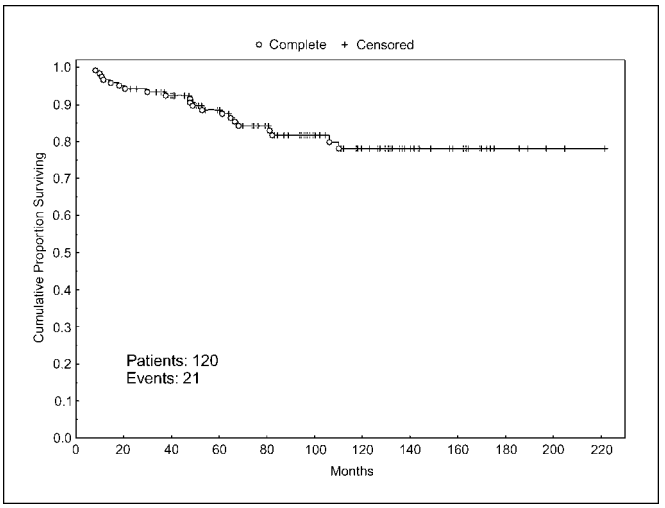

Fig. 2. Event-free survival.

Late cardiovascular events. Overall, 12 (10%) patients developed cardiovascular complications over time (Table 4). Of these, 11 involved the heart and included acute myocardial infarction (5 patients), congestive heart failure (2), valvular stenosis (2), restrictive cardiomyopathy (1), and pericarditis (1); a single event involved a major thoracic vein in a prior irradiation field (innominate vein thrombosis). Altogether, the median irradiation dose to the mediastinum was 41 Gy (range: 36-44 Gy) and the cumulative dose of doxorubicin was 200 mg/m^2 (range: 200-300 mg/m^2). The median age of patients developing a subsequent myocardial infarction was 47 years (range: 16-60 years) and the median time from the end of therapy was 67 months (range: 33-179 months). Valvular stenosis and restrictive cardiomyopathy or pericarditis developed in four patients; all of them had been given mediastinal radiotherapy (36, 40, 36, and 41 Gy, respectively), and the time intervals from the end of radiotherapy were 23, 60, 68, and 24 months, respectively. Two patients concomitantly developed a symptomatic restrictive pulmonary disease (lung fibrosis and mediastinal fibrosis). Two young patients (ages 26 and 40 years) developed a congestive heart failure; both of them had been given a 200 mg/m^2 cumulative dose of doxorubicin and mediastinal irradiation (40 and 44 Gy, respectively). The actuarial risk of late cardiovascular events in our cohort is illustrated in Fig. 4, showing 5- and 12-year cumulative risks of 5.5% and 14%, respectively. Minor cardiac events (not shown in Table 4) included asymptomatic partial bundle branch block in three cases.

Thyroid toxicity. Overall, five patients (all females) developed hypothyroidism and a single male patient a symptomatic hyperthyroidism. The median age of patients developing dysthyroidism was 27 years (range: 23-53 years); all patients had been irradiated to the neck with radiotherapy doses ranging from 36 to 44 Gy. The median time from the end of radiotherapy to dysthyroidism was 74 months (range: 27-107 months) and cumulative risks at 5 and 12 years were 2% and 7%, respectively.

Secondary neoplasms. Secondary neoplasms developed in 6 (5%) patients, consisting of two cases of gastric carcinoma and single cases of breast carcinoma (mucinous), small-cell lung carcinoma, thyroid medullary carcinoma, and diffuse large B-cell lymphoma (Table 5). All patients, but one with gastric carcinoma, developed a secondary neoplasm in an irradiated area (radiotherapy median dose, 36 Gy), and the median time interval from therapy to secondary neoplasia was 45 months (range: 38-122 months). Figure 4 illustrates the actuarial risk of secondary neoplasia in our cohort, with 5- and 12-year cumulative risks of 4% and 8%, respectively. The standardized incidence rate for secondary neoplasia (Table 6) in the whole cohort was 2.6, indicating a significantly higher risk compared with the reference population; the standardized incidence ratio according to gender indicated, however, that the higher risk was limited to females (standardized incidence ratio, 4; $P = 0.003$) and was not significantly increased in males (standardized incidence ratio, 1.55; $P = 0.5$).

Standardized mortality ratio. The standardized mortality ratio (Table 6) was significantly higher than 1 for the entire cohort of patients (5.1; $P = 0.014$) and for both males (2.8; $P = 0.029$) and females (9.4; $P = 0.003$). This indicates that in our cohort, the mortality, corrected for age, sex, and calendar year, was higher than that expected for a reference population.

Child-bearing after therapy. The median age of the 67 women in our cohort was 31 years (range: 15-65 years); 24 (36%) of them were younger than 25 years at the diagnosis of Hodgkin's lymphoma and 59 (88%) were in a potentially reproductive age (<40 years of age). Menstrual abnormalities, with transient amenorrhea, were observed during and/or after the ABVD chemotherapy in 33% of potentially fertile women; no cases of permanent amenorrhea were registered under the age of 25 years. Overall, 10 women (17% of those potentially fertile) became pregnant in one or more occasions after the completion of treatment. The median age of this group was 24 years (range: 18-34 years) at the diagnosis of Hodgkin's lymphoma and 32 years (range: 21-37 years) at the first pregnancy after therapy; five women had more than one pregnancy. Ovary protection with an estrogen-progesterone association had been given during chemotherapy in all cases experiencing a pregnancy, and in all, but one, no significant menstrual abnormalities had been registered after completion of therapy. Altogether, 18 pregnancies were registered; 14 of them went favorably to term and in no instances newborn abnormalities were observed. Among the four abortions, one

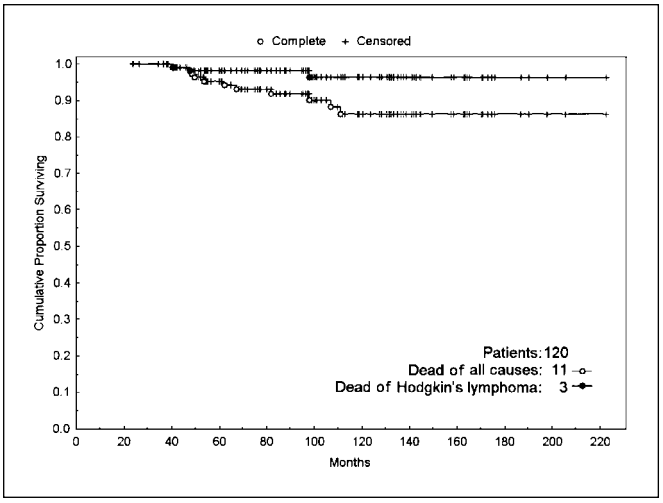

Fig. 3. Overall and cause-specific survival.

Table 3. Characteristics of patients developing pulmonary symptoms after mediastinal radiotherapy

UPN	Sex	Age at Dx of HL (y)	Acute respiratory symptoms	Time from RT (wk)	Early radiologic findings	RT dose (Gy)	Cumulative BLM dose (mg/m^2)	Late sequelae and time from RT (wk)
1	M	19	Dyspnea, cough, hypoxia	10	Pulmonary infiltrates	40	60	Restrictive syndrome (60)
5	F	27	Cough	4	Mediastinitis	40	60	Mediastinal fibrosis (84)
12	F	29	Dyspnea, cough, hypoxia	5	Mediastinitis	40	100	Lung fibrosis (120)
13	M	29	No	—	No apparent	44	80	Mediastinal fibrosis (76)
14	F	27	Cough	2	Mediastinitis	44	80	Mediastinal fibrosis (52)
16	F	21	No	—	No apparent	44	80	Mediastinal fibrosis (123)
17	M	52	No	—	No apparent	44	60	Mediastinal fibrosis (117)
53	M	55	No	—	No apparent	40	80	Mediastinal fibrosis (57)
111	F	30	Dyspnea, cough, hypoxia	12	Pulmonary infiltrates	36	80	Restrictive syndrome (50)

Abbreviations: BLM, bleomycin; Dx, diagnosis; HL, Hodgkin's lymphoma; RT, radiotherapy; UPN, unique patient number.

case was voluntary, one was due to cervical incontinence, with no evidence of hormonal deficiency and/or fetal defects, and the last two cases of spontaneous abortions (in a 34-year-old woman) were followed by a normal pregnancy giving birth to a healthy baby.

Discussion

The long-term results presented in this article extend our prior data on the efficacy of a combined modality approach in favorable early-stage Hodgkin's disease (11) and indicate a 15-year disease-free survival of 90%; these results are comparable with data from other groups using brief ABVD and irradiation for clinical stage IA-IIA Hodgkin's lymphoma in adult patients (5, 10, 12). In spite of a very low tumor-related mortality (3%, actuarial), a sustained excess mortality risk was still observed, with a 78% long-term event-free survival, indicating that a proportion of patients continue to die from causes unrelated to disease progression. The standardized mortality ratio was significantly higher than that expected for a reference population, and this excess mortality was mostly due to the occurrence of secondary neoplasms or fatal cardiovascular diseases.

A nonnegligible fraction of patients experienced nonfatal late complications, mostly related to the use of radiotherapy. Hodgkin's lymphoma survivors who have been treated with chest radiotherapy are at increased risk (relative risk between 2 and 7) of cardiovascular events (16, 17), particularly coronary artery disease. Besides, mediastinal irradiation can cause a variety of cardiovascular complications, including pericarditis, myocardial fibrosis, valvular abnormalities, and conduction disturbances. In our series, the 12-year cumulative risk of cardiovascular complications was 14%, with a median interval of >5 years from the end of radiotherapy and no evidence of a decreasing risk over time. All patients developing restrictive cardiomyopathy and/or valvular defects had received mediastinal irradiation of ≥36 Gy; two of them developed a pulmonary restrictive syndrome, as well. Moreover, asymptomatic conduction disturbances (partial bundle branch block) were documented in three cases, and the long-term significance of this minor complication remains to be determined. A recent Dana-Farber study has documented a variety of unsuspected clinically significant cardiovascular abnormalities in long-term survivors of Hodgkin's lymphoma treated at a young age with mediastinal irradiation and evaluated at a median of 14 years after diagnosis; almost all survivors extensively surveyed had cardiovascular abnormalities, with a particularly high risk for restrictive cardiomyopathy, valvular abnormalities, conduction defects, autonomic dysfunction, and a significantly reduced peak oxygen consumption (18).

The potential pulmonary toxicity of chest irradiation has long been recognized (19), and the hazard of enhanced pulmonary toxicity induced by the combination of bleomycin

Table 4. Characteristics of patients developing late cardiac events

UPN	Sex	Age at Dx of HL (y)	Type of event	Time from therapy (mo)	Mediastinal RT	Dose of RT (Gy)	Cumulative ADM dose (mg/m^2)	Fatal
3	M	16	Myocardial infarction	179	Yes	44	200	No
7	M	60	Myocardial infarction	140	No	—	200	No
9	M	27	Pericarditis	23	Yes	36	200	No
12	F	29	Valvular sclerosis	60	Yes	40	200	No
15	F	40	Congestive heart failure	82	Yes	44	200	No
18	F	26	Congestive heart failure	73	Yes	40	200	Yes
30	M	49	Myocardial infarction	45	No	—	300	No
36	F	53	Valvular sclerosis	68	Yes	36	200	No
50	F	44	Myocardial infarction	67	Yes	36	200	Yes
53	M	55	Restrictive cardiomyopathy	24	Yes	41	200	No
99	F	47	Myocardial infarction	33	Yes	36	300	No

Abbreviations: ADM, doxorubicin; Dx, diagnosis; HL, Hodgkin's lymphoma; RT, radiotherapy; UPN, unique patient number.

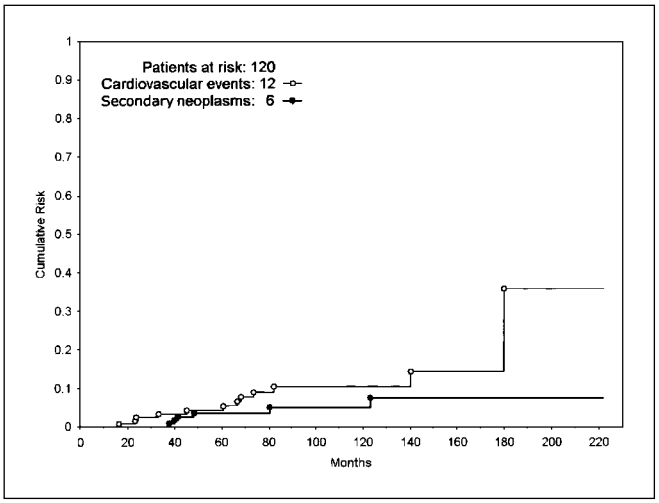

Fig. 4. Actuarial risk of cardiovascular events and secondary neoplasia.

Table 6. Standardized mortality ratio and incidence ratio for secondary neoplasia

	Males	Females	Total
No. patients	53	67	120
Person-years	414.47	560.08	974.55
No. deaths from all causes	4	7	11
Standardized mortality ratio	2.8 (P = 0.029)	9.4 (P < 0.001)	5.1 (P < 0.001)
No. secondary neoplasms	2	4	6
Standardized incidence ratio	1.6 (P = 0.530)	4 (P = 0.003)	2.6 (P = 0.014)

and radiotherapy has extensively been analyzed (20). In our cohort, 8% of patients developed late mediastinal and/or pulmonary fibrotic complications with a pulmonary restrictive syndrome; in none of them did the cumulative dose of bleomycin exceed 100 mg, and in only one case was documented a lung lesion, suggesting bleomycin toxicity. Therefore, as was the case for cardiac toxicity, the major contribution to pulmonary toxicity was derived from radiotherapy.

A substantial contribution to the excess mortality of patients with early-stage Hodgkin's lymphoma derives from the occurrence of secondary neoplasms, mainly in breast, lung, gastrointestinal tract, and soft tissues. Patients treated with radiotherapy have an ~25% risk of developing a second malignancy at 25 years, with no evidence of decreasing risk over time (21–25). In our cohort, the 12-year cumulative risk of secondary neoplasia was 8%, and all tumors, but one, developed in an irradiated area, reinforcing the concept that prior radiotherapy may play a major role in inducing this late event.

The data on fertility preservation and child-bearing potentialities after our short therapy program consolidate the notion that ABVD is devoid of ovary toxicity. The young age at treatment and the adoption of an ovary protection with an estrogen-progesterone association or a gonadotropin-releasing hormone analogue may have played a role in sparing reproductive capacity. A correlation between age at treatment and the risk of amenorrhea has been documented in the German experience (26), together with the use of oral contraceptive to limit ovarian toxicity. We did not observe congenital malformations in the offspring and this supports prior data on favorable pregnancy outcome in long-term survivors after therapy for Hodgkin's lymphoma (27).

The extent and the doses of radiotherapy of our program, although reduced compared with the doses of a radiotherapy alone approach, do not seem to have decreased the risk of late complications; on the other hand, the role of short ABVD chemotherapy in producing late events is likely to have been very limited, as documented by fertility preservation and lack of secondary myelodysplasia/leukemia. In patients with early-stage Hodgkin's lymphoma, data from the German Hodgkin's Study Group (28) and the Milan National Cancer Institute (5) have conclusively shown that, after four cycles of ABVD, involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy. A further attempt at reducing both chemotherapy and radiotherapy in patients with favorable early-stage Hodgkin's lymphoma is being evaluated in an ongoing German study (12). Because even low doses of radiotherapy in a therapeutic range are associated with an increased risk of second cancer, to omit radiotherapy altogether seems to be the only way to avoid radiotherapy-related toxicity in nonbulky early-stage Hodgkin's lymphoma. A randomized study from the Memorial Sloan-Kettering Cancer Center (29) has compared six cycles of ABVD versus six ABVD + adjuvant radiotherapy in nonbulky disease; no significant differences were found in remission duration and freedom from progression and overall survival between the two arms.

Table 5. Characteristics of patients developing a secondary neoplasia

UPN	Sex	Age at Dx (y)	Type of neoplasia	Time from therapy (mo)	Type of RT	Dose of RT (Gy)	Irradiated area	Fatal
17	M	52	Small-cell lung carcinoma	48	Mantle	44	Yes	Yes
22	F	30	Breast (mucinous) carcinoma	38	Mantle	32	Yes	No
35	F	35	Medullary thyroid carcinoma	122	Neck	36	Yes	No
37	F	34	Gastric adenocarcinoma	80	Mantle	36	Yes	Yes
96	M	37	Gastric adenocarcinoma	40	Neck + axilla	36	No	Yes
98	M	67	Diffuse large B-cell NHL (tonsilla and spleen)	41	Neck	36	Yes	Yes

Abbreviations: Dx, diagnosis; NHL, non-Hodgkin's lymphoma; RT, radiotherapy; UPN, unique patient number.

A study from the National Cancer Institute of Canada and Eastern Cooperative Oncology Group (30) has compared ABVD alone (four to six cycles) with a treatment including radiotherapy in patients with limited-stage Hodgkin's lymphoma and found no difference in overall survival; the 5-year freedom from progression was modestly superior in patients receiving radiotherapy, but this advantage was counteracted by deaths from causes other than progression of Hodgkin's lymphoma. As suggested by Commentaries (31–33), both trials establish that cure is achievable with ABVD alone in a very large fraction of patients with limited-stage Hodgkin's lymphoma while holding radiation therapy and avoiding life-long related risks. A positive positron emission tomography imaging after two cycles of chemotherapy has recently been shown to be highly predictive of progression in Hodgkin's lymphoma (34); therefore, in future trials, an early positron emission tomography survey may help define patients who need adjuvant irradiation after short chemotherapy in early-stage nonbulky Hodgkin's lymphoma.

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