Randomized Comparison of ABVD Chemotherapy With a Strategy That Includes Radiation Therapy in Patients With Limited-Stage Hodgkin’s Lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group

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ABSTRACT

Purpose
We report results of a randomized trial comparing ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy alone with treatment that includes radiation therapy in patients with limited-stage Hodgkin’s lymphoma.

Patients and Methods
Patients with nonbulky clinical stage I to IIA Hodgkin’s lymphoma were stratified into favorable and unfavorable risk cohorts. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined-modality therapy if unfavorable risk. Patients allocated to ABVD received four to six treatment cycles.

Results
We evaluated 399 patients. Median follow-up is 4.2 years. In comparison with ABVD alone, 5-year freedom from disease progression is superior in patients allocated to radiation therapy (P = .006; 93% vs 87%); no differences in event-free survival (P = .06; 88% vs 86%) or overall survival (P = .4; 94% vs 96%) were detected. In a subset analyses comparing patients stratified into the unfavorable cohort, freedom from disease progression was superior in patients allocated to combined-modality treatment (P = .004; 95% vs 88%); no difference in overall survival was detected (P = .3; 92% vs 95%). Of 15 deaths observed, nine were attributed to causes other than Hodgkin’s lymphoma or acute treatment-related toxicity.

Conclusion
In patients with limited-stage Hodgkin’s lymphoma, no difference in overall survival was detected between patients randomly assigned to receive treatment that includes radiation therapy or ABVD alone. Although 5-year freedom from disease progression was superior in patients receiving radiation therapy, this advantage is offset by deaths due to causes other than progressive Hodgkin’s lymphoma or acute treatment-related toxicity.

INTRODUCTION

More than 90% of patients with limited-stage Hodgkin’s lymphoma may achieve a durable disease-free state. However, the long-term survival of these patients is also determined by the eventual risks of developing fatal treatment-related toxicities. These toxicities include increased risk of developing acute leukemia, which is associated with use of chemotherapy regimens that include alkylating agents or epipodophyllotoxins, second cancers, and cardiovascular events, which are associated with radiation therapy.
The chemotherapy regimen consisting of doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine (ABVD) provides as good as or better control of Hodgkin’s lymphoma than observed with previous standard chemotherapy regimens, does not include an alkylating agent, and is not associated with the long-term toxicities seen with radiation therapy. We hypothesized that use of this regimen, as a single modality would improve the long-term overall survival of patients with limited-stage Hodgkin’s lymphoma.

**Study Design**

This multicenter non-blinded randomized controlled trial was initiated by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) in 1994. Collaboration with the Eastern Cooperative Oncology Group (ECOG) began in 1996. The primary objective of this trial was to compare the 12-year overall survival of patients with limited-stage Hodgkin’s lymphoma who were treated with chemotherapy consisting of ABVD, or with a strategy that included radiation therapy. This report describes an initial analysis of freedom from disease progression and event-free and overall survivals at 5 years. The trial schema is shown in Figure 1.

The process for patient random assignment was concealed and performed through a computer-generated random number sequence conducted at the central office of the NCIC-CTG. All participating centers received approval from their local research ethics boards and written informed consent was obtained from all participants. Data were held and analyzed by the NCIC-CTG.

**Eligibility and Evaluation of Patients**

Between January 1994 and April 2002, we evaluated 405 patients ages 16 years and older with previously untreated, biopsy-confirmed, limited-stage Hodgkin’s lymphoma. The histologic diagnosis was confirmed by a local reference pathologist and through central pathology review. Limited-stage disease was defined using the principles of the Ann Arbor staging classification; criteria included clinical stage I to IIA disease and absence of bulky disease defined as a mediastinal mass width on a standard chest
radiograph of greater than or equal to one third of the maximum chest wall diameter, or any mass greater than 10 cm. Patients with isolated subdiaphragmatic disease were eligible provided that all evidence of disease was confined to the iliac, inguinal and/or femoral regions; patients with intra-abdominal or splenic disease were ineligible. Patients with low-risk limited-stage Hodgkin’s lymphoma were excluded (Fig 1). Based on assessment by their attending physicians, patients were excluded if there was evidence of lung or cardiac dysfunction, or other general medical problems that would preclude administration of either of the assigned therapies. Patients were also excluded if they had abnormal baseline laboratory values of hematologic, renal or liver function, a known positive antibody test for the human immunodeficiency virus, or a prior or concurrent malignancy (patients with a history of carcinoma-in-situ of the cervix were excluded; patients with adequately treated basal cell carcinoma of the skin were permitted entry). Patients were ineligible if they had undergone a staging laparotomy. Before random assignment, all patients were to be assessed by a hematologist or medical oncologist and a radiation oncologist, with both individuals agreeing that protocol therapy could be administered.

Mandated baseline investigations included a history and physical examination, CBC and erythrocyte sedimentation rate, biochemical assessments of liver and renal function, chest radiograph, and computed tomographic (CT) scanning of the chest, abdomen and pelvis. Optional investigations included bipedal lymphangiography, gallium scanning, bone-marrow aspiration and biopsy, and additional imaging studies if clinically indicated. Laboratory testing was required within 21 days of random assignment; CT scanning was required within eight weeks of random assignment.

Among the 405 patients evaluated, six patients (1.5%) were subsequently considered ineligible (Fig 2). The remaining 399 patients are included in this analysis, which has been conducted according to the intention-to-treat principle. Baseline characteristics of eligible patients are shown in Table 1.

Treatment Protocol

Before random assignment, patients were stratified into favorable and unfavorable risk cohorts (Fig 1) and by treatment center. The prognostic stratification schema was developed and employed to identify patients who would be at higher risk of progressive or recurrent Hodgkin’s lymphoma if treated with radiation therapy alone. This schema was also designed to facilitate achieving a balance of pretherapy risk factors between the two randomly assigned groups. All patients allocated to receive ABVD alone received four treatment cycles with restaging investigations repeated after two and four cycles of therapy. Those achieving a complete or unconfirmed complete remission19 after two treatment cycles, regardless of risk stratification, received a total of four cycles; those not achieving this end point after their second cycle received a total of six cycles. If allocated to receive radiation therapy, patients categorized into the
favorable cohort received subtotal nodal radiation therapy as a single modality where as patients categorized into the unfavorable cohort received combined-modality therapy consisting of two cycles of ABVD followed by subtotal nodal radiation; restaging during this therapy was not performed. The ABVD regimen was administered according to standard dosing and scheduling. Use of granulocyte colony-stimulating factor was permitted according to institutional or provincial guidelines, but was not permitted within the first half of the first treatment cycle or to increase the doses of chemotherapy or shorten the time interval between treatments. Radiation therapy was given by linear accelerator to parallel opposed fields to a midplane dose of 3,500 cGy given in 20 daily fractions. A centralized process for real-time review of radiation treatment prescriptions and fields was completed.

**Assessment of Response and Definition of Study Outcomes**

Responses to therapy were categorized according to the Cotswolds criteria and evaluated by re-examining all abnormal findings recorded at the pretherapy evaluation through use of the same diagnostic modalities used to detect disease before commencing therapy. Patients allocated to receive ABVD alone completed re-evaluations after the second, fourth and, when applicable, sixth

| Table 1. Pretherapy Characteristics of Patients With Limited-Stage Hodgkin’s Lymphoma Treated With a Strategy That Includes Radiation Therapy or ABVD Chemotherapy Alone |
|------------------|------------------|------------------|
| Characteristic    | With Radiation Therapy (n = 203) | ABVD Alone (n = 196) |
| Age at allocation, years | No. % | No. % |
| Median            | 36.7 | 35.0 |
| < 40              | 112 | 55 |
| ≥ 40              | 91  | 45 |
| Sex               |    |    |
| Female            | 87  | 43  |
| Male              | 116 | 57  |
| Stage at diagnosis |    |    |
| IA                | 66 | 33 |
| IIA               | 137 | 67 |
| Histology         |    |    |
| Interfollicular   | 0  | 0  |
| Lymphocyte predominant | 22 | 11 |
| Mixed cellularity | 47 | 23 |
| Nodular sclerosing | 131 | 64.5 |
| Unclassified      | 3  | 1.5 |
| ESR < 50 mm/hour  | 177 | 87 |
| ≥ 50 mm/hour      | 26  | 13 |
| No. of nodal sites of Hodgkin’s lymphoma |    |    |
| < 4               | 186 | 92 |
| ≥ 4               | 17  | 8  |
| Prognostic cohort* |    |    |
| Favorable         | 64  | 32 |
| Unfavorable       | 139 | 68 |

*Prior to random assignment, patients were stratified into favorable and unfavorable risk cohorts. Favorable patients had all of the following characteristics: age younger than 40 years; ESR < 50 mm/hour; lymphocyte predominant or nodular sclerosing histology; and < four nodal sites of Hodgkin’s lymphoma. Patients without any one or more of these characteristics were categorized into the unfavorable cohort.
treatment cycles. Patients allocated to receive radiation therapy completed re-evaluation 1 month after completing radiation therapy; those achieving an unconfirmed complete remission or a partial response underwent a second re-evaluation 3 months after completing radiation therapy. Patients were subsequently assessed 3, 6, and 12 months after completing therapy, and then annually. With annual re-evaluation, repeat CT scanning was performed in patients with clinical features suggesting possible recurrent Hodgkin’s lymphoma.

Freedom from disease progression was measured from the time of random assignment until disease progression. Patients who died without evidence of progressive disease were excluded from this analysis at the time of death. Event-free survival was measured from the time of random assignment until disease progression or death from any cause. Overall survival was measured from the time of random assignment until the time of death from any cause. Deaths occurring in patients with relapsed Hodgkin’s lymphoma that were attributed to a treatment-related toxicity of subsequent therapy (eg, stem cell transplantation) were counted as deaths due to Hodgkin’s lymphoma.

Statistical Analyses

Freedom from disease progression and event-free and overall survivals were calculated with the life-table method of Kaplan and Meier\(^20\) and compared by the log-rank test.\(^21\) CIs for these 5-year outcomes were constructed with SEs determined with Greenwood’s formula.\(^22\)

The primary end point of this trial was overall survival. The trial was designed to detect a 10% improvement in overall survival at 12 years from 80% for patients allocated to radiation therapy in comparison with 90% for patients allocated to receive ABVD. With a power of 80%, and a two-tailed \(P\) value of .05, we determined that a sample size of 450 patients would be required. We anticipated that accrual would require 7.5 years, and that another 7 years of follow-up would be needed.

**Treatment Received**

Treatment received by the 399 eligible patients is shown in Figure 2. Treatment was received as assigned in the protocol by 180 patients (92%) allocated to ABVD. In patients allocated to radiation therapy, treatment was administered as assigned in the protocol to 53 patients (83%) in the favorable cohort and 139 (90%) of the unfavorable cohort patients.

**Treatment Outcomes**

Patient outcomes are shown in Figure 3 and Table 2. With a median duration of follow-up of 4.2 years, freedom
from disease progression is inferior in patients randomly assigned to ABVD ($P = .006$; hazard ratio [HR], 2.6; 5-year survival estimates, 87% vs 93%) and there is a trend toward inferior event-free survival ($P = .06$; HR, 1.7; 5-year survival estimates, 86% vs 88%). No difference in overall survival has been detected ($P = .4$; HR, 0.7) with 5-year survival estimates of 96% (ABVD) and 94% (radiation therapy).

A subset analysis was performed to evaluate the outcomes of patients categorized into the favorable and unfavorable cohorts (Table 2, Fig 4). Among favorable-cohort patients, no differences between randomly assigned groups were detected with respect to any outcome measure. In contrast, among patients categorized into the unfavorable cohort, freedom from disease progression is inferior in patients randomly assigned to ABVD ($P = .004$; 5-year survival estimates, 88% vs 95%). No differences in event-free ($P = .09$) or overall survival ($P = .3$) were detected with 5-year estimates of event-free survival of 85% (ABVD) and 88% (combined-modality therapy), and overall survival of 95% (ABVD) and 92% (combined-modality therapy).

Subset analyses of patients allocated to treatment with ABVD alone failed to detect differences in any outcome measure between patients categorized into the favorable or unfavorable cohorts (Table 2). An additional analysis was performed to evaluate the prognostic significance of achieving a complete or unconfirmed complete remission after two cycles of ABVD. Among the 196 patients allocated to receive ABVD, 69 patients (35%) were assessed as achieving this end point; no differences between those categorized into the favorable (18 of 59 patients; 31%) or unfavorable (51 of 137 patients; 37%) cohorts were detected. Of these 69 patients, 57 (83%) received a total of four cycles of ABVD, as prescribed by protocol; 12 patients (17%) received a total of six treatment cycles with this decision determined by their treating physician. As shown in Figure 5, freedom from disease progression was superior in patients achieving a complete or unconfirmed complete remission after two cycles of therapy ($P = .007$; 5-year survival estimates, 95% vs 81%).

### Causes of Death and Other Morbidity

Fifteen patients have died, including six allocated to ABVD alone and nine to receive radiation therapy. Causes of death are shown in Table 3. Six deaths occurred in patients allocated to receive ABVD: one (due to Hodgkin’s lymphoma) in a patient categorized into the favorable cohort and five in patients categorized into the unfavorable cohort. All nine deaths observed in patients allocated to radiation therapy...
We hypothesized that treatment with ABVD as a single modality would improve the long-term survival of patients with limited-stage Hodgkin’s lymphoma. For long-term survival to be improved, we speculated that disease control would be comparable with standard treatment that includes radiation therapy and that the incidence of long-term toxicities would be reduced, resulting in fewer deaths from other causes.

We observed that, in comparison with patients receiving treatment that includes radiation therapy, treatment with ABVD alone does not provide the same degree of disease control; freedom from disease progression at 5 years was 87% compared with 93% (P = .006). This difference was due to the superior disease control seen in patients stratified into the unfavorable cohort, in which the freedom from disease progression at five years was 95% in patients allocated to receive combined-modality therapy as compared with 88% in patients allocated to receive ABVD alone (P = .004). This difference of 7%, or a number needed to treat of 14.3 patients in order to benefit one patient, needs to be considered in the context of other factors that will influence long-term survival. These include the long-term toxicities associated with the treatments used, and the ability to achieve a state of disease control with second-line therapy. A thorough evaluation of the importance of long-term toxicities in determining the long-term outcomes will require longer follow-up because second cancers and cardiovascular events associated with radiation therapy are particularly observed in the second decade after completing therapy.4,5,7,8,11

Coincident with our trial, other investigators were testing alternative treatment strategies in similar patients. The results of three recent randomized trials have demonstrated that disease control is superior in patients who receive combined-modality therapy consisting of abbreviated chemotherapy with two or three treatment cycles in combination with radiation therapy as compared with extended-field radiation therapy as a single modality.1-3 In one of

### DISCUSSION

We hypothesized that treatment with ABVD as a single modality would improve the long-term survival of patients with...
these trials, the combined-modality therapy included involved-field radiation therapy.\textsuperscript{2} Thus, the standard therapy chosen when we initiated our trial is no longer recommended; treatment with combined-modality therapy that includes involved-field radiation therapy is now considered to be the standard of care.\textsuperscript{24} We anticipated that patients with adverse prognostic features would have a higher risk of progressive Hodgkin’s lymphoma if treated with radiation therapy alone, and therefore stratified patients in our standard therapy group so that higher-risk patients would receive combined-modality therapy. The freedom from disease progression result of 95% at 5 years observed in our unfavorable cohort is comparable to that reported by others,\textsuperscript{1-3} and is superior to that seen in our favorable cohort patients who received radiation therapy, indicating that treating all patients with combined-modality therapy might further increase the difference in control of Hodgkin’s lymphoma in comparison with the group treated with ABVD alone.

Our trial already provides insights into the importance of long-term toxicities in influencing the outcomes. Although the median follow-up is only 4.2 years, nine (60%) of the 15 deaths observed are from causes other than Hodgkin’s lymphoma or acute treatment-related toxicities. As predicted, some deaths (seven, or 47%) have been attributed to second cancers and cardiovascular events. Given these other causes of death, the superior freedom from disease progression observed with treatment that includes radiation therapy has not translated into superior overall survival, even in the analysis evaluating unfavorable cohort patients where standard-arm patients received combined-modality therapy. In that analysis, overall survival at 5 years was 95% in patients allocated to receive ABVD alone compared with 92% in patients receiving combined-modality therapy ($P = .3$). The importance of long-term toxicities is further suggested by the observation of non-fatal second cancers and cardiovascular events. After excluding two cases of basal cell carcinoma in patients treated with radiation therapy, other second cancers were seen in four patients allocated to ABVD (two fatal) and eight patients allocated to radiation therapy (three fatal). After excluding two cases of cardiac events of uncertain significance in patients treated with radiation therapy (new cardiomegaly and exacerbation of atrial fibrillation), cardiovascular events were seen in four patients allocated to ABVD (one fatal) and 10 patients allocated to radiation therapy (one fatal). These data are consistent with the hypothesis on which our trial was based.

New interventions complicate the interpretation of our data. Fewer long-term toxicities associated with radiation therapy may be observed with the use of involved-field radiation therapy. Also, our data demonstrating that freedom from disease progression is superior in patients receiving ABVD who achieve a state of complete or unconfirmed complete remission after two treatment cycles (Fig 5) support testing of new imaging modalities, such as positron emission tomography (PET) scanning, to identify those patients who may be adequately treated with less therapy. Accrual to our trial was completed before use of PET scanning became widely available.

In conclusion, we failed to detect a difference in overall survival between patients randomly assigned to receive treatment that includes radiation therapy or ABVD alone. In comparison with those allocated to receive ABVD alone, superior freedom from progressive disease was observed in patients allocated to receive radiation therapy, and specifically in patients who received combined-modality therapy. This advantage appears to be offset by deaths due to causes other than progressive Hodgkin’s lymphoma or acute treatment-related toxicity. Finally, our data demonstrate that patients receiving ABVD alone who achieve a complete or unconfirmed complete remission after two treatment cycles experience superior long-term disease control in comparison with patients not achieving this end point, and that their 5-year freedom from progressive disease is similar to that observed in patients who receive combined-modality therapy.

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**Authors’ Disclosures of Potential Conflicts of Interest**

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Joseph M. Connors, Inex Pharmaceuticals, Roche Canada. Honoraria: Joseph M. Connors, Roche Canada. For a detailed description of these categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

**REFERENCES**


