Patterns of disease progression and outcomes in a randomized trial testing ABVD alone for patients with limited-stage Hodgkin lymphoma

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Background: In the National Cancer Institute of Canada Clinical Trials Group/Eastern Cooperative Oncology Group HD.6 trial, progression-free survival was better in patients randomized to therapy that included radiation, compared to doxorubicin (Adriamycin/C210), bleomycin, vinblastine and dacarbazine (ABVD) alone. We now evaluate patterns of progression and subsequent outcomes of patients with progression.

Patients and methods: After a median of 4.2 years, 33 patients have progressed. Two radiation oncologists determined whether sites of progression were confined within radiation fields. Freedom from second progression (FF2P) and freedom from second progression or death (FF2P/D) were compared.

Results: Reviewers agreed for the extended (kappa = 0.87) and involved field (kappa = 1.0) analyses. Progression after ABVD alone was more frequently confined within both the extended (20/23 vs. 3/10; P = 0.002) and involved fields (16/23 vs. 2/10; P = 0.02). There was no difference in FF2P between groups [5-year estimate 99% (radiation) versus 96% (ABVD alone)] [hazard ratio (HR) = 3.14, 95% confidence interval (CI) 0.63–15.6; P = 0.14]; the 5-year estimates of FF2P/D were 94% in each group [HR = 1.04, 95% CI 0.41–2.63; P = 0.93].

Conclusion: Treatment that includes radiation reduces the risk of progressive Hodgkin lymphoma in sites that receive this therapy, but we are unable to detect differences in FF2P or FF2P/D.

Key words: chemotherapy, Hodgkin, limited-stage, relapse

introduction

Chemotherapy as a single modality is now a recognized option when treating patients with limited-stage Hodgkin lymphoma [1, 2]. Recognition of this option was facilitated by results of a randomized trial, referred to as HD.6, conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Eastern Cooperative Oncology Group (ECOG) [3]. In this trial, patients were randomized to receive treatment that included radiation or to chemotherapy, as a single modality, consisting of doxorubicin (Adriamycin®), bleomycin, vinblastine and dacarbazine (ABVD). With a median follow-up of 4.2 years, progression-free survival (PFS) was superior in patients allocated to radiation therapy, but no difference in overall survival was detected [3]. Even with this intermediate duration of follow-up, the occurrence of late treatment-related toxicities, including second cancers and cardiovascular events, appeared to be more frequent in those receiving radiation therapy. Thus, the treatment decision process for these patients requires balancing the desire for optimal disease control with avoidance of the risks of late treatment-related toxicities [4]. To further assess this balance, we now report the patterns of disease recurrence observed in patients enrolled onto the HD.6 trial, and review their subsequent clinical course, including placing these outcomes into the broader context of all patients evaluated.

patients and methods

objectives

Our objectives include describing the anatomical patterns of progressive disease seen in patients entered onto the HD.6 trial according to the protocol prescribed or a hypothetical field of radiation therapy and comparing these patterns by randomized group. We also describe the therapy received and outcomes of patients with progressive disease and
compare the freedom from second disease progression (FF2P) and freedom from second progression or death (FF2P/D) by randomized group.

**trial design**

The design of the HD.6 trial has been previously reported [3]. Between 1994 and 2002, we evaluated 405 patients aged 16 and over with previously untreated, biopsy confirmed, limited-stage Hodgkin lymphoma. Limited-stage disease was defined using the principles of the Ann Arbor staging classification [5, 6]; eligibility included clinical stage I-IIA disease and absence of bulky disease. Prior to randomization, patients were stratified into favorable and unfavorable risk cohorts. The prognostic stratification schema was employed to identify patients who would be at higher risk of progressive disease if treated with radiation therapy alone, and does not correspond to that used by others to include patients with bulky and/or stage IIB disease [7]. All patients allocated to ABVD alone received four treatment cycles with re-staging investigations repeated after two and four cycles of therapy. Those achieving a complete or unconfirmed complete remission [6] after two cycles, regardless of risk stratification, received a total of four cycles; those not achieving this endpoint after their second cycle received a total of six cycles. If allocated to radiation therapy (3500 cGy in 20 daily fractions), patients categorized into the favorable cohort received subtotal nodal radiation therapy as a single modality with the field of radiation including the mantle, para-aortic region (to the L4 vertebra) and spleen. Patients categorized into the unfavorable cohort received combined-modality therapy consisting of two cycles of ABVD followed by subtotal nodal radiation that included the mantle, para-aortic region (to the L2 vertebra) and splenic regions. Patients with disease confined to the iliac, inguinal or femoral regions received radiation to an inverted Y field.

Patients were assessed 3, 6 and 12 months after completing post-treatment re-staging, and then annually. With annual re-evaluation, computed tomography (CT) scanning was performed if clinical features suggested possible recurrent disease. The database, held and analyzed by the NCIC CTG, was cleaned and locked in August 2003. Subsequent to locking the database, the NCIC CTG received information regarding one patient, randomized to ABVD, who experienced their second episode of disease progression immediately prior to locking the database. This event is included in the current analysis. No other events occurring prior to locking of the database have been reported. All participating centers obtained approval from their Research Ethics Board and all patients provided written informed consent.

**analysis of treatment failure patterns**

The HD.6 database, which includes the dates of all episodes of disease progression, listings of all treatments given, treatment response and dates of death, was retrospectively analyzed. Copies of pre-treatment case report forms for patients who experienced progressive disease were accessed and sites of original disease transcribed onto a project-specific form. Copies of case report forms detailing sites of progressive Hodgkin lymphoma were similarly accessed and these sites were transcribed onto a second project-specific form. The individual responsible for these transcription processes was blinded to treatment allocation and subsequent treatment received. Copies of the project-specific forms were provided to two radiation oncologists expert in the management of Hodgkin lymphoma for evaluation; these individuals were also blinded to treatment allocation and subsequent treatment received. The radiation oncologists were to assume that all patients had received radiation therapy and were to determine whether the sites of progressive disease were confined ‘Within Field’, ‘Out of Field’ or both ‘Within and Out of Field’ with respect to the radiation therapy field in question. These evaluations were to be performed twice: first by considering the extended field of radiation that was prescribed in the HD.6 protocol, and second by considering a hypothetical involved field of radiation. Differences between the two reviewers were adjudicated through a third expert radiation oncologist.

**definition of study outcomes**

Disease progression confined within the extended field of radiation was defined as recurrences within the radiation field prescribed in the HD.6 protocol. Disease progression confined within the involved field was defined as progression within the hypothetical involved field of radiation that would account for pre-treatment sites and volumes of disease [8]. The FF2P was measured from the time of initial randomization until the date of disease progression or death following a first episode of disease progression; assessment of this secondary outcome was planned in the HD.6 protocol. Patients who died without a first episode of progressive disease were censored from this analysis at the time of death. Deaths occurring in patients with progressive Hodgkin lymphoma that were attributed to a treatment-related toxicity of subsequent therapy (e.g. stem cell transplantation) were counted as deaths due to Hodgkin lymphoma. All analyses were performed using the modified intention-to-treat principle that includes all eligible patients.

As the original analysis of this trial showed that 10 of the 15 deaths observed occurred in patients who had not had a first episode of disease progression, an additional unplanned analysis was performed that counts any death or a second episode of disease progression as an event. This analysis is referred to as FF2P/D and is measured from the time of initial randomization until the date of second disease progression or death.

**statistical analyses**

The kappa statistic was used to assess agreement between evaluators of the sites of disease progression [9]. For the purpose of determining inter-observer agreement, the categories of sites of progression were collapsed into Within Field or other. Sites of disease progression, categorized as Within Field, Out of Field, or Within and Out of Field were compared between randomized groups with use of Fisher’s exact test [10]; FF2P and FF2P/D were calculated with the life-table method of Kaplan and Meier [11] and compared by the log-rank test [12].

**results**

As indicated previously [3], we evaluated 405 patients; 206 were allocated to therapy that included radiation and 199 to ABVD alone. Six patients (1.5%), three in each group, were ineligible. The data for one ineligible patient were included in error in a preliminary presentation of these data in abstract form [13] and are not included in this analysis. Among the 399 eligible patients, there were 33 patients who suffered progressive disease; 10 in those allocated to treatment that included radiation therapy and 23 in those assigned to ABVD alone. As reported previously [3], 41 patients received therapy that differed from that prescribed by protocol according to their randomized allocation; no cases of disease progression occurred among these patients. As also previously reported, 15 patients have died. Ten of these patients, including seven allocated to treatment that included radiation and three to ABVD, died without experiencing a first episode of disease progression.

**sites of disease progression**

Agreement between assessors was excellent for both the protocol prescribed extended (kappa = 0.87) and the physical and radiation fields.
hypothetical involved field (kappa = 1.0) analyses. The assessors differed in two cases (6%) and these were resolved by adjudication. Sites of progression are summarized in Table 1. For the analysis evaluating protocol prescribed extended field radiation, disease progression was confined to Within Field in 20 of the 23 patients (83%) allocated to ABVD alone and three of the ten patients (30%) allocated to radiation therapy (P = 0.0002). These patterns of Within Field progression translate to rates of 10.2% in the 196 patients allocated to ABVD alone compared with 1.5% in the 203 patients allocated to therapy that included radiation. Similar findings were obtained when sites of progression were evaluated using a hypothetical involved field of radiation. Disease progression was confined to Within Field in 16 patients (70%) allocated to ABVD compared with two patients (10%) who were allocated to radiation therapy (P = 0.02). These patterns of progression translate to overall rates of Within Field progression of 8.2% in ABVD alone patients and 1.0% in patients allocated to radiation.

Among the 203 patients allocated to radiation therapy, 64 were categorized into the favorable cohort and assigned to receive radiation therapy alone. Six of these patients suffered disease progression, with two having this progression confined within the protocol prescribed extended field of radiation. Among the 139 unfavorable cohort patients who were allocated to combined-modality therapy, four experienced progressive disease with one having this progression confined within the prescribed extended field of radiation. Among the 196 patients allocated to ABVD alone who experienced disease progression, eight were treated with radiation therapy as a single modality. This includes six patients who had disease progression at a single nodal site and two patients with more than one site. Four of these eight patients, two from each category, subsequently experienced a second episode of disease progression and three have died

<table>
<thead>
<tr>
<th>Table 1. Sites of progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy ≥ ABVD (n = 10)</td>
</tr>
<tr>
<td>Extended field analysis (protocol prescribed)</td>
</tr>
<tr>
<td>Infield only</td>
</tr>
<tr>
<td>Outfield only</td>
</tr>
<tr>
<td>Both infield and outfield</td>
</tr>
<tr>
<td>Involved field analysis (hypothetical)</td>
</tr>
<tr>
<td>Infield only</td>
</tr>
<tr>
<td>Outfield only</td>
</tr>
<tr>
<td>Both</td>
</tr>
</tbody>
</table>

Of the 203 patients allocated to treatment that included radiation therapy, 10 experienced disease progression in comparison with 23 patients in the group of 199 who were allocated to receive ABVD alone.

second-line treatments are summarized in Tables 2 and 3. Including all therapies, 17 of the 23 patients with disease progression after ABVD alone remain alive and have not suffered a second episode of disease progression. For the 10 patients who suffered disease progression after initially receiving radiation therapy, eight remain alive without having suffered from further disease progression. As shown in Fig. 1A, and with a median follow-up of 4.2 years, the estimated 5-year FF2P is 96% in 196 patients initially allocated to ABVD alone and 99% in 203 patients allocated to radiation therapy [hazard ratio (HR) = 3.14, 95% confidence interval (CI) 0.63–15.6; P = 0.14]. As shown in Fig. 1B, the 5-year FF2P/D was 94% in both groups (HR = 1.04, 95% CI 0.41–2.63; P = 0.93).

As shown in Tables 2 and 3, several types of second-line therapy were given, including a crossover to therapy initially prescribed for the other randomized group. Among the 23 patients allocated to ABVD alone who experienced disease progression, eight were treated with radiation therapy as a single modality. This includes six patients who had disease progression at a single nodal site and two patients with more than one site. Four of these eight patients, two from each category, subsequently experienced a second episode of disease progression and three have died (two of Hodgkin lymphoma

Figure 1. Freedom from second disease progression (FF2P; A) and freedom from second progression or death (FF2P/D; B) in 399 patients randomized to treatment that includes radiation or ABVD alone. Patients who died before a first disease progression were censored at the time of death in determining FF2P and are included as events in FF2P/D.
and one of non-Hodgkin lymphoma). The other 15 patients received some form of chemotherapy, including two as part of combined modality therapy and seven as part of autologous stem cell transplantation. Two of these patients have experienced further disease progression; no deaths were observed.

Among the 10 patients initially assigned to treatment that included radiation who experienced disease progression, nine subsequently received chemotherapy, including two who received this treatment along with autologous stem cell transplantation. Eight of these nine patients did not experience further disease progression; one patient suffered disease progression and died from this. One other patient was not given further treatment and died of progressive Hodgkin lymphoma.

**Discussion**

The HD.6 trial was based on the hypothesis that, in comparison with therapy that includes radiation, treatment with ABVD alone would improve the long-term overall survival of patients with limited-stage Hodgkin lymphoma. We hypothesized that a major factor contributing to this improvement would be a reduction of late effects related to radiation therapy, including cardiovascular events and second malignancies. We anticipated that detecting improvement in overall survival would require 12 years of follow-up. While longer periods of follow-up will be required to evaluate this endpoint, knowledge of the nature of, and outcomes from, a first episode of disease progression; one patient suffered disease progression and died from this. One other patient was not given further treatment and died of progressive Hodgkin lymphoma.

**Table 2.** Outcomes of second therapy for patients with disease progression after initial treatment that included ABVD alone

<table>
<thead>
<tr>
<th>Modality used for first progression</th>
<th>Number alive with no second progression</th>
<th>Number alive with second progression</th>
<th>Number died of progressive Hodgkin lymphoma</th>
<th>Number died of other cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation alone (N = 8)</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chemotherapy alone (n = 2)</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combined modality (n = 6)</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Autologous stem cell transplantation (n = 7)</td>
<td>5</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 3.** Outcomes of second therapy for patients with disease progression after initial treatment that included radiation

<table>
<thead>
<tr>
<th>Modality used for first progression</th>
<th>Number alive with no second progression</th>
<th>Number alive with second progression</th>
<th>Number died of progressive Hodgkin lymphoma</th>
<th>Number died of other cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone (n = 7)</td>
<td>6</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Autologous stem cell transplantation (n = 2)</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No therapy (n = 1)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

As previously reported, disease control was superior in patients receiving radiation therapy [3]. The estimated 5-year PFS was 93% in those receiving radiation versus 87% in those receiving ABVD (P = 0.006). This difference was due to the advantages seen in the cohort receiving combined-modality therapy; in comparison with those receiving ABVD, the 5-year PFS was 95% versus 88% (P = 0.004). With our current analysis, we confirm that the superior disease control seen with radiation therapy is directly attributable to this treatment. Disease progression confined within the field of radiation therapy prescribed in the HD.6 protocol was observed in 20 patients allocated to ABVD alone and in only three treated with radiation (P = 0.002). Furthermore, our data are consistent with a previous report [14] and preliminary descriptions of ongoing studies [15, 16] that indicate disease control is achieved in a high number of patients who receive combined-modality therapy that includes radiation that is limited to the involved field. When the disease progression patterns of patients included in HD.6 were evaluated according to a hypothetical involved field of radiation, disease progression within this field was observed in 16 patients assigned to ABVD and in only two who were treated with radiation (P = 0.02).

In comparison with PFS, FF2P is likely to be a better predictor for eventual death due to progressive Hodgkin lymphoma. In addition, because subsequent treatments may also be associated with long-term toxic effects, deaths from other causes may also be more frequently observed in patients who experience an episode of disease progression. Our current analysis, performed with a median follow-up of 4.2 years and a range of 1.3 to 9.4 years, failed to detect a difference in the FF2P between randomized groups. The 5-year FF2P estimates were 99% (two events) versus 96% (six events) in the radiation and ABVD arms, respectively (P = 0.14). With respect to risks of failing to detect inferior outcomes in patients treated with ABVD alone, this analysis is conservative in that deaths occurring prior to a first episode of disease progression were not counted as events; these patients were censored at the time of death. There were seven such deaths in patients treated with
radiation in comparison with three in patients allocated to ABVD. To account for these deaths, we performed an unplanned analysis of FF2P/D. In this analysis, the 5-year estimates were 94% with nine events in each of the groups ($P = 0.93$).

The specifics of treatment for progressive disease were not defined in the HD.6 protocol. Investigators were encouraged to consider providing radiation therapy to patients with disease progression after treatment with ABVD alone. Our analysis includes only 23 patients who had suffered disease progression after receiving ABVD alone, and these patients were treated in a heterogeneous manner. We are therefore not able to reach conclusions regarding what constitutes optimal therapy. Specifically, we were not able to demonstrate that radiation therapy as a single modality would be sufficient therapy, as four of eight patients treated in this manner remain free of second progression or death as compared with 13 of 15 treated with some form of chemotherapy with or without radiation treatment. The concept of tailoring therapy according to the specifics of the pattern of disease progression, including provision of radiation therapy as a component of treatment for patients with disease progression that is limited to previously involved areas, may be appropriate. Such an approach has been described in a case series of 11 patients who suffered progressive disease after receiving ABVD alone [17]. In that series, 9 of 11 patients relapsing after ABVD alone were alive and free from second progression with a median follow-up of 64 months. These patients were treated according to defined criteria: five patients with a single supradiaphragmatic disease site, low erythrocyte sedimentation rate and absence of B symptoms were treated with mantle radiation and six others who did not satisfy these criteria were treated with second-line chemotherapy and autologous stem cell transplantation. The design of that trial differs from ours in that the patients with progressive disease were extracted from a case series that included patients with B symptoms and bulky disease.

The long-term survival of patients with limited-stage Hodgkin lymphoma will continue to depend on the balance between disease control and the occurrence of late effects. In evaluating this balance, the duration of follow-up of patients entered into the HD.6 trial is intermediate. We have previously reported that late effects appear to be more frequent in patients assigned to radiation therapy, but this observation must be tempered by the fact that the radiation administered in HD.6 would now be regarded as excessive. The theme of mutually exclusive abilities to evaluate both the most current of therapies and have long-term follow-up will remain as future therapies evolve. With this report, we have demonstrated that in comparison with chemotherapy alone, radiation therapy reduces the risk of disease progression in initially involved sites but that with an intermediate duration of follow-up, differences in the eventual control of Hodgkin lymphoma have not been detected.

**conflict of interest statement**

None declared.

**references**