
Treatment-Associated Leukemia Following Testicular Cancer

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Background: Men with testicular cancer are at an increased risk of leukemia, but the relationship to prior treatments is not well characterized. The purpose of our study was to describe the risk of leukemia following radiotherapy and chemotherapy for testicular cancer. **Methods:** Within a population-based cohort of 18 567 patients diagnosed with testicular cancer (from 1970 through 1993), a case-control study of leukemia was undertaken. Radiation dose to active bone marrow and type and cumulative amount of cytotoxic drugs were compared between 36 men who developed leukemia and 106 matched control patients without leukemia. Conditional logistic regression was used to estimate the relative risk of leukemia associated with specific treatments. All *P* values are two-sided. **Results:** Radiotherapy (mean dose to active bone marrow, 12.6 Gy) without chemotherapy was associated with a threefold elevated risk of leukemia. Risk increased with increasing dose of radiation to active bone marrow (*P* for trend = .02), with patients receiving radiotherapy to the chest as well as to the abdominal/pelvic fields accounting for much of the risk at higher doses. Radiation dose to active bone marrow and the cumulative dose of cisplatin (*P* for trend = .001) were both predictive of excess leukemia risk in a model adjusted for all treatment variables. The estimated relative risk of leukemia at a cumulative dose of 650 mg cisplatin, which is commonly administered in current testicular cancer treatment regimens, was 3.2 (95% confidence interval = 1.5–8.4); larger doses (1000 mg) were linked with statistically

significant sixfold increased risks. **Conclusions:** Past treatments for testicular cancer are associated with an increased risk of leukemia, with evidence for dose-response relationships for both radiotherapy and cisplatin-based chemotherapy. Statistically nonsignificant excesses are estimated for current radiotherapy regimens limited to the abdomen and pelvis: Among 10 000 patients given a treatment dose of 25 Gy and followed for 15 years, an excess of nine leukemias is predicted; cisplatin-based chemotherapy (dose, 650 mg) might result in 16 cases of leukemia. The survival advantage provided by current radiotherapy and chemotherapy regimens for testicular cancer far exceeds the small absolute risk of leukemia. [J Natl Cancer Inst 2000;92:1165–71]

Men with testicular cancer are at increased risk of leukemia (1); however, the contribution of radiotherapy and chemotherapy to risk is not well characterized (2). Although 20- to 300-fold risks of leukemia have been reported after chemotherapy for testicular cancer (3–8), most estimates have been based on few cases. No study has quantified the role of radiotherapy. Since testicular cancer is largely curable, with a 5-year relative survival rate of more than 95% (9), an understanding of treatment factors that contribute to secondary leukemia, with its associated high mortality rate (1), assumes clinical importance. Moreover, significant increases in testicular cancer incidence worldwide (10) underscore the need to quantify the late effects of treatment in this growing population. To this end, we evaluated the risk of leukemia in relation to therapy for testicular cancer among more than 18 000 patients reported to eight population-based cancer registries in North America and in Europe.

PATIENTS AND METHODS

Study Subjects

A case-control investigation of secondary leukemia was undertaken within a group of 18 567 1-year survivors of testicular cancer diagnosed during the period from January 1, 1970, through December 31, 1993, and reported to population-based cancer registries (11) in Iowa, Connecticut, New Jersey, Ontario (Canada), Denmark, The Netherlands, Sweden, and Finland. Patients with extragonadal germ cell tumors were excluded from the study. For each subject, cancer incidence data were searched for subse-

quent diagnoses of acute leukemia, chronic myeloid leukemia (CML), or myelodysplastic syndrome (MDS). Chronic lymphocytic leukemia has not been associated with prior chemotherapy or radiation therapy and was not included. In an effort to capture all possible cases of MDS, mortality files and/or hospital discharge records were examined to identify patients with an underlying cause of death or discharge diagnosis of severe anemia or other blood disorder. For all hematologic malignancies, clinicopathologic materials, including reports of bone marrow aspirates and biopsies, were reviewed to confirm diagnoses. The 36 eligible case patients, who derived from cancer incidence files (*n* = 34) or other sources described above (*n* = 2), included 15 with acute myeloid leukemia, eight with MDS, eight with acute lymphoblastic leukemia, and five with CML. All diagnostic entities are subsequently referred to as leukemia. Eight case patients from previous reports (4,6) were included to ensure complete information from the cancer registries in Denmark and in The Netherlands.

For each case subject with documented leukemia, three control patients were selected by stratified random sampling from the defined cohort, except in New Jersey, where two control patients were chosen for each of two case patients. Matching factors were age and calendar year of testicular cancer diagnosis, registry, and survival without a second malignant neoplasm at least as long as the period between the occurrence of testicular cancer and leukemia in the case patient. This type of case-control methodology has been used extensively in previous analytic studies of second cancers (12–16).

Data Collection

Standardized abstract forms were used to gather demographic and medical record information for all study subjects, including data on all therapy for testicular cancer during the matched time interval. Sources included hospitals providing initial treatment, local medical centers, radiotherapy departments, and offices of private physicians. Information on dose and duration of administration was abstracted for platinum derivatives, all alkylating

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agents, and etoposide. For other cytotoxic drugs, gathered information was restricted to dates and duration of administration. For 25 of 26 patients who received platinum-based chemotherapy, information on dose was available from medical records. For the remaining subject (a control patient), cumulative dose was imputed from the mean dose given to other control patients who received the same regimen.

External-beam radiotherapy, typically to para-aortic and pelvic regions, was administered to 101 patients; six men also received alkylating agent chemotherapy. In addition to the abdominal and pelvic fields, radiotherapy for 17 men from 1970 through 1980 included chest irradiation (mean dose to mediastinum, 35.0 Gy); three additional patients received extended-field (abdomen, pelvis, and chest) radiotherapy and alkylating agent chemotherapy. For patients who received radiation therapy limited to the abdomen and pelvis without alkylating agents, the average treatment doses were lower (30.7 Gy) for seminoma patients than for men with nonseminomatous tumors (35.4 Gy), consistent with the greater radiosensitivity of the seminoma cell type. The average radiation doses to the abdomen and pelvis were similar for seminoma patients treated before and after 1980 (30.6 and 31.0 Gy, respectively). Throughout the time period of study, eight (13%) of the patients with seminoma received an average treatment dose of less than 25.0 Gy to the abdomen and pelvis, 11 (18%) received 25.0–29.9 Gy, 21 (35%) received 30.0–34.9 Gy, 16 (27%) received 35.0–39.9 Gy, and four (7%) received 40.0 Gy or more. Daily radiotherapy logs for each patient were used to calculate the dose to 17 partitions of active bone marrow (e.g., pelvis, sacrum, and thoracic spine) (17); the doses were then weighted and summed to yield one overall average dose in accord with previous studies (12–16). The radiation dose to active bone marrow was correlated with the average treatment dose to the abdomen and pelvis (correlation coefficient [r] = .72; P = .0001).

Statistical Analysis

Conditional logistic regression was used to estimate the relative risk (RR) of leukemia associated with specific treatments by comparing the exposure histories of the case patients with those of individually matched control patients (18,19). Risk was assumed to be of the form $\exp(\beta \times z)$, where z is either an indicator variable for a treatment or a continuous variable indicating the dose of radiation to active bone marrow or amount of cytotoxic agent (e.g., 650 mg cisplatin). Two-sided P values and 95% confidence intervals (CIs) were based on the likelihood ratio statistic.

Because most patients had received radiotherapy or chemotherapy, it was not possible to construct a reference group of subjects treated with surgery only. Thus, for categorical analyses (see Tables 2 and 3), patients who received an average radiation dose of less than 7.5 Gy to total active bone marrow without alkylating agents were combined with those who were treated either with surgery alone or with nonalkylating agent chemotherapy alone to provide a larger reference group for the calculation of RRs. Resultant estimates may be somewhat conservative but will be less unstable than those derived from using the small number of patients who received surgery alone as the referent. The radiation dose to active bone marrow was also treated as a continuous

variable (see text and Table 4); this approach uses the dose at all levels and does not require the specification of a referent group. Although the radiation dose to active bone marrow remains the most relevant measure of leukemogenic exposure, to facilitate clinical interpretation, selected analyses were also conducted by use of the average treatment dose to the abdomen and pelvis, with an emphasis on risk prediction for doses (25–30 Gy) currently recommended for early-stage seminoma (20).

For categorical analyses, patients were divided into four mutually exclusive treatment groups: radiotherapy without alkylating agents, alkylating agents without radiotherapy, both radiotherapy and alkylating agents, and no radiotherapy or alkylating agents. No patient in the latter group (the referent category) received etoposide. Subjects were considered to be exposed to alkylating agents if they received treatment for at least 1 month (12,13,15,21). Since platinum derivatives generate interstrand DNA cross-links similar to bifunctional alkylating agents (22), they are considered together and were included for initial analyses. Men were further categorized according to total chemotherapy history based on the use of platinum derivatives or assumed high-risk alkylating agents such as chlorambucil (13). Given the weak leukemogenicity of cyclophosphamide at low doses (13–15), patients who received this agent in addition to platinum were grouped in terms of the latter drug. Treatment groups were designated *a priori*. The carboplatin dose (one patient) was converted to a cisplatin-equivalent amount by division by four (23), with cumulative exposure expressed in terms of absolute dose, an analytic approach used in prior studies of secondary leukemia (12–16). Additional analyses were conducted to adjust for the administration of etoposide, which has been linked in some studies to secondary leukemia (4,5,8). The cumulative dose of etoposide was expressed in milligrams per square meter to permit comparisons with prior investigations (4,5,7,8,24). The absolute excess risk of leukemia among 10 000 testicular cancer patients followed for 15 years was estimated with the use of methods that were described previously (15).

RESULTS

The average age at diagnosis of testicular cancer was 39 years. More than 80% of the men (118 of 142) were less than 50 years of age, with 39% (56 of 142) diagnosed after 1980 (Table 1). Most subjects (30 [83%] case patients and 97 [92%] control patients) had early-stage disease (stages I and II). Secondary leukemia developed an average of 6.8 years (median, 5.0 years) after diagnosis of testicular cancer, with 25% occurring after 1 decade (maximum latency, 17.3 years). Four of the 36 case patients relapsed after initial therapy for testicular cancer and received salvage treatment; 34 were in clinical remission at the time of secondary leukemia diagnosis. Survival after leukemia diagnosis was poor (median, 8.4 months; range, 0.1–103 months; 31 deaths). The same proportion (61%) of

case and control patients was treated with radiotherapy (resulting in >7.5 Gy active bone marrow dose; mean dose, 12.6 Gy) without alkylating agents or platinum; the average dose of radiation to active bone marrow for these case and control patients was 13.6 Gy (range, 8.6–23.8 Gy) and 12.3 Gy (range, 7.9–22.9 Gy), respectively.

Treatment of testicular cancer with radiotherapy alone (no chemotherapy), which resulted in a dose of 7.5 Gy or more to active bone marrow, was associated with a threefold increased risk (95% CI = 0.7–22) of leukemia compared with the referent group (Table 2). Fivefold nonsignificant excesses of leukemia followed treatment that included alkylating agents with or without radiotherapy.

Radiotherapy

For men with testicular cancer treated with radiotherapy alone (n = 86), the risk of leukemia increased with increasing radiation dose to active bone marrow (P for trend = .02) (Table 3). Patients whose treatment was limited to abdominal and pelvic fields (mean dose to active bone marrow, 10.9 Gy; average treatment dose, 32.7 Gy) had a statistically nonsignificant 2.9-fold risk of leukemia compared with the referent group; men who also received chest radiotherapy (mean dose to active bone marrow, 19.5 Gy) had an 11-fold risk that was statistically significant. Within this latter group, chest radiotherapy was largely given prophylactically (all seven case patients and eight of 10 control patients). Because larger dose radiation to active bone marrow was strongly correlated with extended-field radiotherapy (all eight patients who received ≥ 20 Gy to active bone marrow had additional chest radiotherapy), the separate contributions of high-dose and large-field irradiation could not be evaluated. The trend of increasing leukemia risk with increasing radiation dose to active bone marrow was no longer significant (P = .52) when patients who received extended-field radiotherapy were excluded.

When radiation dose to active bone marrow was treated as a continuous variable, the predicted RR of leukemia at a dose of 10 Gy for patients given radiotherapy without alkylating agents was 3.7 (95% CI = 1.2–13). The risk of leukemia associated with a radiation dose of 10 Gy was 2.9, 14.1, 4.2, and 0.2 at less than 5, 5–9, 10–14, and 15 or more years, respectively, after diagnosis of testicular cancer,

Table 1. Characteristics of men with secondary leukemia (case patients) and matched control patients among 18 567 subjects with testicular cancer*

| Characteristic | Case patients (n = 36) | | Control patients (n = 106) | |
|---|------------------------|----|----------------------------|----|
| | No. | %† | No. | %† |
| Cancer registry | | | | |
| Connecticut | 2 | 6 | 6 | 6 |
| Denmark | 9 | 25 | 27 | 25 |
| Finland | 1 | 3 | 3 | 3 |
| Iowa | 3 | 8 | 9 | 8 |
| The Netherlands | 6 | 17 | 18 | 17 |
| New Jersey | 2 | 6 | 4 | 4 |
| Ontario (Canada) | 8 | 22 | 24 | 23 |
| Sweden | 5 | 14 | 15 | 14 |
| Age at diagnosis of testicular cancer, y | | | | |
| <30 | 11 | 31 | 31 | 29 |
| 30–39 | 11 | 31 | 33 | 31 |
| 40–49 | 8 | 22 | 24 | 23 |
| ≥50 | 6 | 17 | 18 | 17 |
| Calendar year of testicular cancer diagnosis‡ | | | | |
| 1970–1974 | 10 | 28 | 30 | 28 |
| 1975–1979 | 11 | 31 | 35 | 33 |
| 1980–1984 | 8 | 22 | 23 | 22 |
| 1985–1993 | 7 | 19 | 18 | 17 |
| Stage of testicular cancer | | | | |
| I/II | 30 | 83 | 97 | 92 |
| III/IV | 6 | 17 | 9 | 8 |
| Histologic type of testicular cancer§ | | | | |
| Germ cell tumor, seminoma | 25 | 69 | 62 | 58 |
| Germ cell tumor, nonseminoma¶ | 10 | 28 | 43 | 41 |
| Other# | 1# | 3 | 1** | 1 |
| Latency, y†† | | | | |
| <2 | 5 | 14 | 14 | 13 |
| 2–4 | 13 | 36 | 38 | 36 |
| 5–9 | 9 | 25 | 27 | 25 |
| ≥10 | 9 | 25 | 27 | 25 |
| Treatment of testicular cancer‡‡ | | | | |
| Radiotherapy; no alkylating agents§§ | 22 | 61 | 65 | 61 |
| Alkylating agents; no radiotherapy | 8 | 22 | 15 | 14 |
| Alkylating agents and radiotherapy | 2 | 6 | 4 | 4 |
| Other | 4 | 11 | 22 | 21 |

*Matching variables included registry, age, and calendar year of testicular cancer diagnosis. Three control patients were selected for each leukemia patient, except in New Jersey, where two control patients were chosen.

†Percentages may not sum to 100 because of rounding.

‡Dates for diagnosis of testicular cancer varied slightly by registry, with patients diagnosed through December 31, 1991, in Connecticut, Denmark, and New Jersey; through December 31, 1992, in Ontario and Sweden; and through December 31, 1993, in Finland, Iowa, and The Netherlands. All patients with testicular cancer had to survive at least 1 year to be eligible for the study.

§Lymphomas of the testis were excluded.

||International Classification of Diseases for Oncology (27) (ICD)-O morphology codes 9060–9063.

¶ICD-O morphology codes 9070–9073, 9080–9085, and 9100–9102.

#Includes one germ cell tumor, not otherwise specified (NOS).

**Includes one carcinoma, NOS.

††Represents interval between diagnosis of testicular cancer and leukemia for case patients and comparable interval for matched controls (*please refer to text for details*). The leukemias and myelodysplastic syndromes were further classified as acute lymphoblastic leukemia (n = 8), chronic myeloid leukemia (n = 5), acute nonlymphocytic leukemia (ANLL)—M1 (n = 4), ANLL—M2 (n = 3), ANLL—M3 (n = 1), ANLL—M4 (n = 3), ANLL—not otherwise specified (NOS) (n = 4), refractory anemia with excess blasts (n = 4), chronic myelomonocytic leukemia (n = 1), and myelodysplastic syndrome—NOS (n = 3) (25,26).

‡‡Exposure was defined as treatment with alkylating agents for more than 1 month or radiotherapy that resulted in an average dose to total active bone marrow of 7.5 Gy. Since platinum compounds produce intrastrand and interstrand DNA cross-links similar to those of bifunctional alkylating agents (22), they are considered together with alkylating agents. All patients except three with disseminated disease also underwent orchiectomy. The name of the alkylating agent was specified for 28 of 29 patients (all 10 case patients and 18 of 19 control patients).

§§The same proportion of case and control patients was treated with radiotherapy (resulting in an active bone marrow dose of 7.5 Gy or higher; mean dose, 12.6 Gy) without alkylating agents or platinum; the average dose of radiation to active bone marrow for these case and control patients was 13.6 Gy (range, 8.6–23.8 Gy) and 12.3 Gy (range, 7.9–22.9 Gy), respectively.

|||Includes all case and control patients who received an average radiation dose of less than 7.5 Gy to total active bone marrow and/or treatment with nonalkylating agent chemotherapy. No patient in this group received etoposide.

Table 2. Risk of leukemia associated with treatment of testicular cancer*

| Treatment | Case patients | Control patients | Matched relative risk | 95% confidence interval |
|--------------------------------------|---------------|------------------|-----------------------|-------------------------|
| No alkylating agents or radiotherapy | 4 | 22 | 1.0† | — |
| Radiotherapy; no alkylating agents‡ | 22 | 65 | 3.1 | 0.7–22 |
| Alkylating agents;§ no radiotherapy | 8 | 15 | 5.0 | 1.0–40 |
| Alkylating agents and radiotherapy | 2 | 4 | 5.1 | 0.5–58 |

*Exposure was defined as treatment with alkylating agents for more than 1 month or radiotherapy that resulted in an average dose to total active bone marrow of 7.5 Gy. The category of alkylating agents includes platinum derivatives.

†The referent group.

‡No patient in this category received etoposide.

§Chemotherapy included cisplatin and etoposide (five case patients and five control patients), cisplatin and chlorambucil (two case patients), or other cisplatin-based regimens (one case patient and nine control patients). For one control patient, the type of alkylating agent was not specified.

||Chemotherapy included cisplatin without etoposide (one case patient and three control patients) or cyclophosphamide without other alkylating agents (one case patient and one control patient).

Table 3. Risk of leukemia following testicular cancer according to radiation dose to total active bone marrow (ABM) and radiation treatment fields*

| Dose or field | Case patients | Control patients | Mean dose to ABM, Gy† | Matched relative risk | 95% CI |
|-------------------------|---------------|------------------|-----------------------|-----------------------|---------|
| Dose to ABM, Gy | | | | | |
| <7.5 | 4 | 22 | 1.9 | 1.0‡ | — |
| 7.5–9.9 | 7 | 16 | 9.1 | 3.5 | 0.6–27 |
| 10–14.9 | 8 | 36 | 11.6 | 2.4 | 0.4–20 |
| 15–19.9 | 3 | 8 | 17.0 | 4.9 | 0.5–57 |
| ≥20 | 4 | 4 | 22.4 | 19.7§ | 1.5–590 |
| Radiotherapy fields | | | | | |
| Abdomen, pelvis | 15 | 54 | 10.9 | 2.9 | 0.6–21 |
| Abdomen, pelvis, chest¶ | 7 | 10 | 19.5 | 11.2 | 1.5–123 |

*The table is restricted to patients whose treatment did not include alkylating agents. One patient (a control) for whom radiation dose to active bone marrow could not be estimated was excluded from both the table and the analysis. CI = confidence interval.

†Represents the average dose to active bone marrow among all patients (both case and control patients) in designated category.

‡The referent group for all comparisons.

§Test for trend with radiation dose treated as a continuous variable; $P = .02$; the relative risk for greater than or equal to 15 Gy was 7.8 (95% CI = 1.1–79).

||Includes patients who received radiotherapy to para-aortic and inguinal/iliac lymph nodes. The average treatment dose to the abdomen and pelvis for all of the patients in this category was 32.7 Gy (median, 30.5 Gy). The average treatment doses were lower (30.7 Gy) for seminoma patients than for men with nonseminomatous tumors (35.4 Gy), consistent with the greater radiosensitivity of the seminoma cell type.

¶Includes patients who received radiotherapy to para-aortic and inguinal/iliac lymph nodes and either prophylactic (seven case patients and eight control patients) or therapeutic (two control patients) chest irradiation.

but the differences in risk by time were not statistically significant (P for heterogeneity = .44). We found no evidence that risk varied by cancer registry ($P = .34$), patient age (<40 versus ≥40 years; $P = .92$), or histologic type of testicular cancer (seminoma versus nonseminoma, $P = .99$), but statistical power to detect these differences was small.

Analyses in which the average radiation treatment dose, rather than the dose to active bone marrow, was entered as a continuous variable were also conducted. For patients given radiotherapy limited to the abdomen and pelvis (no chest), the

estimated RR of leukemia associated with a treatment dose of 25 Gy was 2.2 (95% CI = 0.6–12). Corresponding risks at treatment doses of 30 and 35 Gy were 2.5 (95% CI = 0.5–19) and 2.9 (95% CI = 0.4–30), respectively. None of these risk estimates was statistically significant.

Chemotherapy

Treatment of testicular cancer included alkylating agents for 29 patients, with drug name specified in 28 (10 case patients and 18 control patients). Twenty-six men received platinum-based chemotherapy, with cisplatin given to 25 sub-

jects and cisplatin and carboplatin given to one patient (Table 4). Primary therapy for seven case patients who did not receive chlorambucil consisted of a median of five cycles of cisplatin, at a median total dose per cycle of 200 mg (range, 90–375 mg); men in the control group received a median of four cycles of cisplatin, at a median total dose per cycle of 200 mg (range, 90–230 mg). Additional courses of platinum-based chemotherapy were given to two case patients who relapsed. Combination chemotherapy included cisplatin and etoposide in five case patients and in five control patients. The median cumulative dose of cisplatin was considerably higher for case patients (1525 mg) than for control patients (815 mg); the median cumulative doses of etoposide were 1897 mg/m² (range, 540–4054 mg/m²) for case patients and 1613 mg/m² (range, 1383–1829 mg/m²) for control patients, respectively. Therapy included both cisplatin and chlorambucil, an established leukemogen (13), in two case patients (no control patients) who were considered separately in the analysis.

For the 24 patients who received platinum-based chemotherapy without chlorambucil, the cumulative amount of cisplatin was related to increased risks of leukemia (P trend for dose = .001) in a multivariate model that adjusted for radiation dose. The total amount of etoposide did not contribute to leukemia risk ($P = .64$) when doses of cisplatin and radiation were taken into account. Patients who were given etoposide, however, also received higher doses of cisplatin, making it difficult to separate the individual contributions to risk. No effect was observed for bleomycin. Based on a model in which the cisplatin dose was treated as a continuous variable, the predicted risk of leukemia associated with a cumulative dose of 650 mg, commonly administered in current treatment regimens (28), was 3.2 (95% CI = 1.5–8.4). Larger total doses (e.g., 1000 mg cisplatin) were associated with higher risks (RR = 5.9; 95% CI = 2.0–26). On the basis of small numbers, combined treatment with chlorambucil and platinum appeared to increase leukemia risk, whereas no excesses (RR = 0.9) were observed for chemotherapy regimens that did not include either platinum or chlorambucil.

DISCUSSION

This is the largest investigation of leukemia following testicular cancer to in-

Table 4. Summary of chemotherapy treatments of testicular cancer*

| Chemotherapy | Case patients | Control patients |
|-------------------------------|---------------|------------------|
| Platinum; no chlorambucil† | 7 | 17 |
| Cumulative cisplatin dose, mg | | |
| Mean | 1480 | 760 |
| Median | 1480 | 783 |
| Range | 360–3090 | 210–1360 |
| Duration of therapy, mo | | |
| Mean | 7.5 | 4.9 |
| Median | 4.9 | 3.5 |
| Range | 2.9–15.5 | 2.0–13.8 |
| Platinum; chlorambucil‡ | 2 | 0 |
| Cumulative cisplatin dose, mg | | |
| Mean/median | 470 | — |
| Range | 160–780 | — |
| Duration of therapy, mo | | |
| Mean/median | 16.9 | — |
| Range | 6.0–27.7 | — |
| Other chemotherapy§ | 1 | 1 |
| Duration of therapy, mo | 18.0 | 25.0 |

*Treatment categories shown in the table are mutually exclusive and reflect the total chemotherapy history for the patient within the matched time interval at risk. Exposure was defined as treatment with alkylating agents for more than 1 month. Designated cytotoxic agents were usually given in combination with other drugs. All risks are adjusted for radiation dose by means of a continuous variable; one patient (a control) for whom radiation dose to active bone marrow could not be estimated was excluded from the analysis. Excluded from the table is one control patient for whom the type of alkylating agent was not specified.

†Includes all patients who received platinum without chlorambucil. Other cytotoxic drugs given to two case patients (one with acute nonlymphocytic leukemia [ANLL]—not otherwise specified [NOS]; and one with acute lymphoblastic leukemia [ALL]) and 12 control patients in this category included bleomycin and vinblastine; three of these control patients subsequently received regimens that included cyclophosphamide (cumulative dose, 2300, 2500, and 3100 mg, respectively). Five case patients (two with myelodysplastic syndrome—NOS and one each with ANLL—M1, ANLL—M4, and ANLL—NOS) and five control patients received combination chemotherapy that included cisplatin and etoposide; in this latter category, therapy also included bleomycin in four case patients and three control patients and carboplatin in one case patient.

‡Includes one case patient (with ANLL—M1) who received cisplatin, chlorambucil, doxorubicin, dactinomycin, and vinblastine and one case patient (with ALL) who received cisplatin, chlorambucil, doxorubicin, dactinomycin, vinblastine, cyclophosphamide, and bleomycin. The cumulative dose of chlorambucil in the two subjects was 235 and 730 mg, respectively.

§Includes one case patient (diagnosis: refractory anemia with excess blasts) who received cyclophosphamide, vinblastine, and vincristine and one control patient who was given cyclophosphamide, 5-fluorouracil, methotrexate, and vincristine. The cumulative dose of cyclophosphamide in the two subjects was 27 600 and 11 400 mg, respectively.

clude quantitative measures of radiation dose to active bone marrow for individual patients as well as cumulative amount of chemotherapeutic agents. Among more than 18 000 men with testicular cancer, a significant dose-dependent risk of leukemia was associated with past radiotherapy techniques and small but nonsignificant excesses for modern regimens that limit treatment to the abdomen and pelvis. Our investigation reinforces awareness that large increases in the radiotherapy field size for testicular cancer that result in high doses to large volumes of bone marrow can be associated with statistically significantly elevated risks of leukemia. Furthermore, we found evidence for an association between increasing cumulative dose of cisplatin and excess leukemias that adds to the growing body of knowledge that identifies platinum derivatives as human leukemogens.

Chemotherapy for testicular cancer has been associated with secondary leukemia risks that range from 20- to 300-fold (3–8); however, most estimates were based on only one to four cases. With 24 patients given platinum-based chemotherapy in our study, strong evidence is provided for a relationship between cumulative dose of cisplatin and leukemia risk and parallels findings among ovarian cancer patients, in whom the largest leukemia risk (RR = 7.6) occurred after total amounts of 1000 mg or more (12). Men in our population-based study received a wide range of cumulative doses of cisplatin, although amounts, on average, were considerably larger than those currently used. For example, in view of modern therapeutic recommendations (28), it is likely that newly diagnosed testicular cancer patients with an average body surface area (about 1.8 m²) receive a

cumulative cisplatin dose in the range of 540–720 mg, less than the average dose (1480 mg) administered to the case patients in our study but similar to the average total dose (760 mg) given to the control patients. The estimated 3.2-fold risk of leukemia at lower cumulative doses (e.g., 650 mg) of cisplatin in our study is consistent with the 3.3-fold risk (95% CI = 1.1–9.4) observed among ovarian cancer patients who received a median total cisplatin dose of 600 mg (12). Persistent chromosomal aberrations have been reported in peripheral blood lymphocytes of testicular cancer patients treated with platinum without etoposide (29), and platinum is carcinogenic *in vitro* and in laboratory animals (30).

We were unable to detect a relation between etoposide and increased leukemia risk when radiation and cisplatin were taken into account, but only five case patients and five control patients were administered etoposide at relatively low amounts. As reviewed by van Leeuwen (31), chemotherapy with etoposide and cisplatin for testicular cancer has been linked with excess leukemias (4,5,7,8), usually at high cumulative doses of etoposide (3000 mg/m²) (4) compared with the lower total doses in our study (median, 1900 mg/m²), which are similar to the less than 2000-mg/m² dose used today (28,31). In addition, a recent comprehensive survey (24) of clinical trial data concluded that the total dose of epipodophyllotoxins was not a pivotal predictor of leukemia risk, reporting that the 6-year cumulative risk of secondary leukemia among patients who received 1500–2999 mg/m² was small (0.7%). Pedersen-Bjergaard and Rowley (32) have postulated that cytostatic drugs with different mechanisms of action, i.e., direct binding to DNA (cisplatin) and inhibition of DNA-topoisomerase II (etoposide), may have a synergistic effect in leukemogenesis, but we were unable to address this issue.

Although the leukemogenicity of ionizing radiation has been well established (33), to our knowledge, our investigation is the first to link convincingly past radiation treatments for testicular cancer to leukemia, to quantify this risk in terms of dose to bone marrow, and to estimate risks associated with modern radiotherapy practices. Although registry-based surveys (1,34) have suggested previously that increased risks of leukemia may follow radiotherapy for testicular cancer, a

role for subsequent chemotherapy could not be excluded. Nonsignificant excesses of leukemia were observed following radiation for testicular cancer in several clinical series, albeit based on few cases (3,6,35). In addition to the paucity of analytic data, in a review of more than two decades of the scientific literature, Redman et al. (3) identified a total of nine patients with leukemia following radiotherapy alone for testicular cancer; a more recent compilation describes only leukemias associated with chemotherapy (2).

Although the sparse number of cases treated with surgery alone limited the precision with which we could quantify leukemia excesses, the small risk of leukemia after radiotherapy limited to abdominal and pelvic fields for testicular cancer (average treatment dose, 32.7 Gy) is similar to the twofold risks reported after therapeutic radiation for cancers of the cervix and endometrium or benign gynecologic disorders (33). When large doses of radiotherapy are delivered to concentrated areas of bone marrow, as during treatment for cervical cancer, cell killing is thought to predominate over cell transformation, and the resultant risks of leukemia are much lower than predicted based on the studies of atomic bomb survivors, who received lower doses to the entire body (33). Similarly, among patients given either large-field chest irradiation for breast cancer (15) or radiotherapy for Hodgkin's disease (16), dose-dependent risks of leukemia analogous to those observed among our patients whose treatment included chest radiotherapy have been reported.

The wave-like pattern of excess leukemias that we observed following radiotherapy for testicular cancer is qualitatively similar to patterns observed among atomic bomb survivors and patients treated for cervical cancer (33), the largest studies to date to quantify the leukemogenicity of ionizing radiation (36). Among atomic bomb survivors, leukemia rates were highest within 10 years of exposure and tapered gradually so that excess risks were observed for four decades. In contrast, after treatment of cervical cancer, little radiation excess was apparent beyond 10 years.

Because our investigation was conducted among patients in the general population covered by well-defined reporting areas, it is unlikely to suffer from selection biases that may be operant in hospital or clinic-based series. The large

international study base of more than 18000 patients treated as early as 1970 allowed us to quantify the radiation effect over a range of doses to active bone marrow. A limitation of our investigation is the small numbers of leukemias in various subgroup analyses, which restrict the inferences that can be made regarding patterns by age at exposure, latency, and interaction with chemotherapy. It is recognized that studies of late effects of treatment, including second cancers, are inherently limited to retrospective examination. Any untoward sequelae associated with state-of-the-art therapy (37) emerge only with time. Thus, the clinical relevance of our results, based on patients diagnosed with testicular cancer between 1970 and 1993, should be interpreted in light of modern therapeutic practices. Treatments for a portion (20%) of patients in our study included mediastinal radiotherapy, which is no longer used. Furthermore, in the 1990s, chemotherapy regimens commonly include etoposide to a greater extent than in years past (28), and smaller radiotherapy fields and lower doses are used (37). For example, the average treatment dose to the abdomen and pelvis for patients with seminoma in our study (30.7 Gy; maximum, 45 Gy) is considerably higher than the 25–30 Gy recommended by Bosl et al. (20) to treat newly diagnosed patients today. Thus, continued monitoring of late effects as treatments evolve (38,39) should be encouraged.

While physicians should be reminded of the possible late toxicity of treatment of testicular cancer, especially in patients with an otherwise good prognosis, the relatively low excess risk of leukemia is reassuring. For example, in terms of absolute risk, we estimate that, of 10000 testicular cancer patients treated with 25–30 Gy radiotherapy to the abdomen and pelvis and followed for 15 years, an excess of nine to 11 leukemias might be expected; cisplatin-based chemotherapy, given at a cumulative dose of about 650 mg, might result in up to 16 excess leukemias over a comparable period. Thus, when balancing risks and benefits of current radiotherapy techniques or platinum-based chemotherapy in the treatment of testicular cancer, the substantial improvement in survival far exceeds any small absolute excess risk of leukemia.

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