Hodgkin Lymphoma

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Evaluation of the Risk of Therapy-Associated Complications in Survivors of Hodgkin Lymphoma

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Given the improvements in survival of patients with Hodgkin lymphoma (HL) in the last three decades, quantification of the late effects of successful treatment has become critical. Since the highest incidence rates of HL occur at ages 20 to 34 years, large numbers of patients remain at lifelong risk for the late effects of treatment. Deaths due to second cancers are now the most common cause of mortality among long-term survivors of HL, followed by cardiac disease. Risk measures of these and other late sequelae, however, can vary markedly between investigations, depending on the types of treatment, the rigor with which epidemiologic study designs are applied, ascertainment of events of interest, the duration and completeness of follow-up, and consideration of competing risks. Further, numerous influences apart from therapy can affect late effects, including patient age, sex, race, lifestyle factors (tobacco, alcohol, diet), comorbidities, and the underlying cancer process. In the future, it will become increasingly important for health-care providers to be able to critically evaluate the risk of late effects in HL survivors, which will include a working knowledge of various epidemiologic study designs and risk measures and an ability to judiciously review the medical literature. In this article, the methods, significance and caveats in calculating and reporting risks of complications of treatment for HL are reviewed.

Introduction

In 2005, the Institute of Medicine and the National Research Council of the National Academies issued the report *From Cancer Patient to Cancer Survivor: Lost in Transition.*[1] Recommendations in this report included the conduct of additional studies to measure the prevalence and risk of late effects. Thus, it becomes increasingly important for health-care providers to understand the terminology and methods used to evaluate the risk of late sequelae, and to be able to critically evaluate research results. The need is especially important for clinicians who care for patients with Hodgkin lymphoma (HL), in view of the burgeoning number of reports which document late effects (reviewed in Hoppe et al[2]). Given an overall 5-year relative survival rate of 85% for patients with HL,[3] and the fact that the highest incidence rates occur between ages 20 and 34 years, large numbers of patients remain at lifelong risk for the late effects of treatment. In the U.S. alone, there are about 120,000 HL survivors. Although second primary cancers are now the leading cause of death in patients with HL,[4,5] survivors are also at elevated risks for cardiac disease, pulmonary disorders, endocrine dysfunction, and other sequelae (reviewed in Hoppe et al[2]).

Accurate quantification of therapy-associated complications is important for the management of patients with HL, in order to permit clinicians to balance treatment efficacy against acute and chronic sequelae, and to develop risk-adapted follow-up strategies. Considerable confusion, however, exists with regard to the optimal measure(s) for reporting the risk (or magnitude) of therapy-related complications. Risk can be framed in several terms, including relative risk and cumulative risk. Frequently, it is difficult for health-care providers to understand the underlying methods that are used to generate various risk measures and thus to critically evaluate overall study quality. In many cases, various surveys produce divergent risk estimates due to other factors that affect the risk of late effects, including patient age, sex, race, the types and doses of administered

radiotherapy and chemotherapy, lifestyle factors (tobacco, alcohol, diet) and the length and completeness of follow-up. Thus, it can be complicated to accurately compare risk measures between studies. For example, estimates of the cumulative absolute risk of breast cancer among young women with HL have ranged from 4.2% to 34% at 20 to 25 years of follow-up (reviewed in Travis et al[6]), and many have not taken into account the influence of competing causes of mortality. Thus, an understanding of the derivation of various risk measures and an ability to critically review new research studies is important to enable healthcare providers to balance the risks and benefits of treatment and to provide targeted follow-up. In this article, the methods, significance and caveats in calculating and reporting risks of complications of treatment for HL are reviewed. Although examples largely focus on second cancers, the methods are transferable to the evaluation of other treatment complications.

Methods to Evaluate Treatment Complications

Although various case reports or small series can alert clinicians to a possible link between treatment and an adverse outcome, they can not prove causality. For example, second cancers may not necessarily represent an adverse effect of therapy but can reflect numerous other factors such as lifestyle choices, including tobacco, alcohol and diet; environmental causes; host factors such as genetic susceptibility, immune function, and hormonal status; chance; and interactions between influences.[7,8] Thus, critical to any evaluation of second cancers is an assessment of whether their occurrence exceeds expectation; if so, the influence of other risk factors must be ruled out before increased risks can be attributed to treatment.

Several epidemiologic study designs are used to obtain estimates of risk. Two commonly used designs include the cohort and case-control studies. In the cohort approach, a well-defined group of patients is followed for the outcome of interest (**Table 1**). In the case-control design, treatment given to patients who develop a second cancer (or other outcome) is compared with the treatment given to matched controls who do not develop a second cancer.

Cohort studies

Sources of cohort studies include population-based cancer registries such as the National Cancer Institute (NCI) SEER Program and the nationwide Scandinavian cancer registries. Advantages of these registries include large numbers of patients, which permit the detection of even small risks, and the ability to evaluate second cancer patterns by site, latency, sex, and ages at first and second cancer diagnoses. In addition, the observed and expected numbers are based on the same population. Since all patients are included, there is no selection or referral bias. The disadvantages of population-based cancer registries are that treatment data are limited, and when present, generally consist only of the initial course of therapy defined according to generic categories such as radiation or chemotherapy. In addition, underreporting of second cancers results from migration of patients from SEER areas, although this is generally not a problem in nationwide registries. Thus, the major utility of population-based registries is that they enable a global evaluation of site-specific second cancer risk and are a practical foundation for nested case-control studies in which detailed analyses of treatment factors can be conducted. In a number of settings, cohorts of cancer survivors can also be linked to administrative claims data, such as the Medicare database,[9] in order to evaluate treatment complications; it should be noted, however, that this linkage is inherently limited to older patients.

Other cohorts in which the risk of therapy-related complications can be assessed include clinical trial databases and hospital-based tumor registries. Advantages of the former include the availability of detailed information for protocol therapies and the theoretical advantage that one can make direct comparisons between treatment efficacy and therapy-related complications in randomized groups of patients. Disadvantages include the fact that there are usually few or no data on subsequent therapy, and frequently there is limited follow-up and incomplete reporting of outcomes, especially long-term events. Moreover, the relatively small number of patients in many series does not permit the statistical power to accurately assess the risk of adverse sequelae. Hospital-based tumor registries offer the advantage of larger numbers of patients and the availability of treatment data, whereas drawbacks include variability in follow-up and outcome reporting. In addition, the risk of any late effects, including second cancers, is overestimated if follow-up is more complete for patients with complications who re-enter the health care system than for patients who remain healthy.

Several measures of risk can be derived from cohort studies. A frequently used comparison in relation to the general population in studies of second cancers is the observed-to-expected ratio, also commonly referred to as the standardized incidence ratio (SIR). In this calculation, person-years of observation in the cohort are used to estimate the expected numbers of second cancers, based on population incidence rates, according to 5-year age groups, sex, and 5-year calendar year periods. The observed number of second cancers is then compared with the number expected

Table 1. Epidemiologic study designs to evaluate the risk of late effects.

Cohort study: well-defined group of patients followed for late effects

Sources of cohort studies include:

- Population-based cancer registries
- Clinical trial databases
- Hospital-based cancer registries

Case control study: treatment is compared between patients with and without the late effect of interest

(**Table 2**). Another type of comparison with the general population is the absolute excess risk (AER), which consists of subtracting the expected number of second cancers from the observed number, dividing by the person-years at risk, and then multiplying by 10,000. This measure provides an overall estimate of the excess number of second cancers per 10,000 patients per year, and can also be calculated according to latency periods and age and sex groups. In order to allow for more careful adjustment of the effects of age at first and second cancer diagnosis, latency and calendar year considerations, multivariable statistical methods have been successfully used.[6]

In reviewing cohort studies, it is important to realize even a high relative risk can translate into a low absolute risk if the specific second cancer (or other outcome) is rare in the general population. For example, in an international registry-based study of HL, the SIR of acute myeloid leukemia was 22-fold, whereas the AER was only 6.3 excess cases per 10,000 patients per year[10] (**Table 3**). The AER provides perhaps the best measure of which second malignancies contribute the greatest cancer burden to a population, and also provides a valid comparison with other late sequelae.

Another measure of outcomes in cohort studies includes actuarial estimates. These procedures use censored data methods to evaluate in-cohort risk, e.g., such as the percentage of patients diagnosed with a second cancer in a specified time interval. One example is cumulative incidence (or cumulative risk)[11] (**Table 2**). In this instance, it is important to use methods that take into account competing risks, since for example, a patient with HL may die of cardiovascular disease before a second cancer is diagnosed. Armitage et al[12] recently provided a comprehensive discussion of estimation methods that take into account competing risks in comparison with alternative methods in the context of treatment-related leukemias. Even when actuarial estimation procedures are used, the risk of late effects can still be overestimated if follow-up is less complete for patients who remain healthy and who do not re-enter the health-care system. A third type of measure is the Cox proportional hazard analysis, which permits evaluation of the effect of selected variables, such as treatment, on specific outcomes. This analysis adjusts for follow-up time, age, sex, and other factors, and yield estimates of the incidence rate (or hazard) ratios.

Case-control studies

In the typical retrospective cohort study, treatment data are collected for all patients, which is time-consuming and expensive. An alternative efficient approach is the nested case-control study, in which the cohort serves as a mechanism to identify the outcome of interest; this design has been most frequently used in studies of second cancers. The controls are a random matched sample of patients without a second cancer derived from the same cohort. Detailed treatment factors can then be compared between the two groups, including the dose-response relation between radiation or cumulative drug dose and second cancer excesses.

Other measures of risk that can be derived from nested case-control studies include the AER of second cancers associated with a given treatment. This calculation requires

Table 3. International Lymphoma Study*—secondary leukemia: SIR versus AER.

- Observed leukemias = 169
- Expected leukemias = 7.86
- SIR (= O/E) = 169/7.86 = 21.5
- PY of follow-up: 255,778
- AER = $\frac{O - E}{PY} = \frac{169 - 7.86}{255{,}778} \times 10{,}000$

  = 6.3 excess cases per 10,000 pt per y

Abbreviations: SIR, standardized incidence ratio; AER, absolute excess risk; O, observed; E, expected; pt, patient; PY, person year
*Dores G et al.[10]

Table 2. Cohort studies: examples of measures of risk.

Comparisons with the general population

- Standardized incidence ratio (SIR), also referred to as observed-to-expected (O/E) ratio (or relative risk)
  - Population incidence rates are used to estimate expected numbers of events, taking into account age, gender, and calendar year
  - Observed number of events (e.g., second primary cancers) compared with number expected
  - If no increased risk exists (i.e., observed = expected), then SIR or O/E = 1
- Absolute excess risk (AER)
  - AER = $\frac{\text{observed} - \text{expected second cancers}}{\text{No. of person-years at risk}} \times 10{,}000$ = Excess no. of second cancers per 10,000 patients per year
  - If no increased risk (i.e., observed = expected), then AER = 0

Cumulative incidence (cumulative risk)

- Percentage of patients diagnosed with event of interest in specified time interval
  Example: 25-y cumulative incidence of solid tumors among 32,591 patients with Hodgkin lymphoma was 11.7%.*

*Dores G et al.[10]

the availability of basic cohort information, such as person-years of follow-up and underlying cancer incidence. The AER in this case consists of the relative risk obtained from the case-control study minus 1, multiplied by the expected number of cancers in the cohort, multiplied by the number of years at risk, then multiplied by 10,000. This approach was used by Curtis et al[13] to derive the excess number of leukemias among 10,000 patients with breast cancer followed for 10 years after treatment with cyclophosphamide, or 5 excess cases.

Limitations of nested case-control studies include overmatching. The purpose of matching is to ensure similarity of the cases and controls on confounding variables. Overmatching may result when a matching factor is not a confounder, such as stage of cancer, since stage is frequently a surrogate for therapy; thus, inclusion of this factor is akin to matching on treatment, which can then not be examined as a main effect in the analysis. The results of overmatching include a reduction in statistical power to detect associations, larger standard errors and wider confidence intervals. Estimates of the relative risk should not be biased. Another limitation of case-control studies is that the analytic methods require specification of a referent group. Although an optimal group would consist of nonexposed patients, this is unlikely in studies of patients with cancer. One solution is to choose a low-dose exposure group, realizing that the resultant risks may then be underestimates.[14] An alternative solution is to use continuous variables to model second cancer risk whenever possible.[15]

Example of Risk Measures: Second Primary Breast Cancer

An example of a nested case-control study is a large multicenter investigation of breast cancer after HL that was conducted by the NCI in collaboration with cancer registries in Iowa, Ontario, Sweden, Denmark, Finland, and the Netherlands.[14] In the first step, the cohort was defined as all women diagnosed with HL between 1965 and 1994 at age 30 years or younger, who survived 1 or more years, and who were reported to one of the indicated population-based cancer registries. The final cohort consisted of 3817 patients, of whom 105 developed a second primary breast cancer. In the next step, matched controls without breast cancer were selected from the underlying cohort by stratified random sampling. For all patients and controls, detailed data on chemotherapy, radiation dose to the area of the breast in which cancer developed, radiation dose to ovaries, and other factors were collected. In the analysis, relative risks were compared between treatment groups by using standard conditional logistic regression programs. Radiation breast dose or 4 or more gray (Gy) was associated with a significantly increased 3.2-fold risk of breast cancer compared with patients who received lower doses and no alkylating agents. Note that the referent group consisted of women who received less than 4 Gy to the area of the breast in which cancer developed in the patients (or to the corresponding area in the controls). Thus, as pointed out by the study authors,[14] the point estimate of 3.2 likely represents a minimal estimate of risk. Risk of breast cancer increased to 8-fold at > 40 Gy (*P* trend with radiation dose < .001). The finding of a strong dose-response relationship adds to the likelihood that the radiation was a significant contributor to breast cancer risk, i.e., not a confounding variable. Increased risks persisted for more than 25 years after radiotherapy (*P* trend with radiation dose = .03), a pattern consistent with the late carcinogenic effects of radiation. Treatment with alkylating agents alone resulted in an overall 40% reduction in breast cancer risk, with a significant trend in decreasing breast cancer risk observed with an increasing number of alkylating agent cycles (*P* trend = .003). A low risk (relative risk, 0.5) was also observed among women who received 5 Gy or more to ovaries compared with those who received lower doses. Breast cancer deficits paralleled the percentage of women who became menopausal after treatment, showing the importance of hormonal stimulation on breast cancer risk following HL chest radiotherapy. Other results can be found in the original article.[14]

The increasing awareness of the large risk of breast cancer following therapy for HL at a young age has created a need for informed counseling. Estimates of the cumulative risk of breast cancer among young women treated for HL at age 30 years or younger, however, have been sparse and inconsistent, spanning 4.2% to 34% at 20 to 25 years after therapy (reviewed in Travis et al[6]).

Most estimates have not taken into account the influence of alkylating agent therapy, which can lower breast cancer risk, or the effect of competing causes of mortality. Accurate projections of breast cancer risk, as available for women in the general population,[16] are important to evaluate the disease burden among the growing population of HL survivors treated with past regimens and to facilitate the development of risk-adapted long-term follow-up recommendations. Estimates of the cumulative risk of breast cancer among women treated for HL at age 30 years or younger were recently provided in terms of measures of radiation dose and chemotherapy, which are available from medical records.[6] The estimates also took into account age and calendar year of HL diagnosis, age at counseling, baseline breast cancer incidence rates, and competing causes of mortality. For example, for an HL survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4%, 11.1%, and 29.0%, respectively. Cumulative risks were lower in women also treated with alkylating agents. In comparison, in the general population, the absolute risks of breast cancer in white women from age 20 years to ages 30, 40, 50, and 60 years are, respectively, 0.04%, 0.5%, 2.0%, and 4.3%. The researchers[6] cautioned that the risk estimates are most relevant for HL survivors treated with past regimens, and should be used with considerable caution in patients treated with more recent approaches,

including limited-field radiotherapy and/or ovary-sparing chemotherapy. As the number of HL survivors grows, there will be an ongoing need for the provision of these types of estimates for various late effects, even as therapies are refined. Moreover, quantification of late effects for successful therapies of the past remains highly relevant for long-term HL survivors and health-care providers.

Comment

Well-designed studies hold great promise to accurately quantify the risk of complications associated with HL and its treatment.[8] The establishment of transdisciplinary clinical and research programs[1,8] will provide the underpinnings required to advance this field and to provide evidence-based clinical practice guidelines and follow-up procedures. Clinicians will increasingly be called on to understand and communicate the resultant risk measures to HL survivors and their families.

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