Breast Cancer After Hodgkin Disease
Hope for a Safer Cure

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F or more than a century, Hodgkin disease (HD) has served as a paradigm for developing modern oncology concepts. Yet the success of using radiotherapy, chemotherapy, or both for cure of a formerly lethal disease has not come without a price.1-3 Even though control of HD in early-stage and overall survival is approximately 90% at 10 years,4 survival is decreasing with more years of observation, primarily due to a higher than expected number of deaths from second malignancies. At 20 years after diagnosis, the cumulative risk of developing second cancers is approximately 10%, exceeding the cumulative risk of dying from the primary early-stage disease.5

For women whose HD was successfully treated at a young age, the main long-term concern is the increased risk of breast cancer.6 During the last decade, multiple studies6 have documented and characterized the risk of breast cancer after HD, and have established 3 facts. First, the increased risk of breast cancer is undoubtedly associated with the use of radiation.7 Radiotherapy alone had been the standard treatment and primary curative modality for HD through the 1970s and early 1980s. Irradiating all lymph node regions, regardless of clinical involvement with HD, has been standard practice, and relatively high doses (>40 Gy) have been used.7 Consequently, a substantial amount of breast tissue has been exposed to either the full prescribed dose or to an attenuated dose (at field margins or under the lung shields) in almost all women receiving radiotherapy for HD.

Second, the increased risk of breast cancer is age-related, with the highest risk associated with treatment at ages 10 years to 20 years. The risk remains significantly increased until age 25 years or 30 years, and disappears thereafter.2

Third, the increased risk is manifested late, the median time from HD treatment to breast cancer is 15 years, and only few events have been reported at the first decade after HD. This explains why the increase in risk of breast cancer became statistically apparent only about 10 years ago.1,2,5,8

However, several critical issues regarding the increased risk of breast cancer have remained unknown or controversial, including the magnitude of the risk as related only to treatment, the impact of radiation dose and exposed breast volume on the risk, and the effect of chemotherapy in either enhancing or decreasing the risk. These issues are of biological interest, have direct relevance to evaluating the risk of current practice, may influence the design of new strategies for treatment of HD, and possibly may support interventions to reduce risk of breast cancer in women previously treated with radiation that resulted in breast exposure.

In this issue of THE JOURNAL, Travis and colleagues9 from 13 centers in 7 countries provide important data that help decipher most of these issues. Their case-control study included 105 women who developed breast cancer within a cohort of more than 38001-year female survivors of HD diagnosed at age 30 years or younger. Unique to this study is the inclusion of patients who received a very low dose of radiation (<4 Gy) or no radiation to the breast area where breast cancer developed. This approach allowed the isolation of treatment factors as well as the analysis of the relationships between risks associated with radiation and chemotherapy doses.

For all patients who received radiotherapy alone (>4 Gy) the relative risk (RR) of breast cancer was 3.2 and increased to 8.0 in the group receiving the highest dose of radiation. Although this risk is significant, it is at the lower end of the previously reported range of RRs (ie, large studies have reported RRs ranging from 2 to 450).10,11 In the largest long-term follow-up study of second neoplasms in survivors of HD, which included data from 16 cancer registries of more than 35000 patients, the RR for breast cancer in women was 2.0 and the absolute excess risk was 10.5.10 Unfortunately, RRs, absolute risks, and actuarial risks are often cited without detailing specifics that could have influenced the findings (ie, length of follow-up for the group and for the individuals; age group, age-incidence, and actuarial risk of the malignancy in an untreated population; and quality of follow-up, which may result in event overestimation).8

In the study by Travis et al,9 the reference point (RR=1.0) consists of patients with breast cancer diagnosed after treatment of HD using low-dose or no radiation, thus allowing

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isolation of the treatment effect of radiation dose, chemotherapy, or ovarian ablation (by radiation), and the combination of radiation and chemotherapy. Indirectly, this approach also allows for disregarding the influence of genetic and environmental factors that may be shared by both diseases, and also provides for elimination of HD risk factors (ie, immunosuppression) that are not completely related to treatment and could influence the RR when calculated in reference to a healthy population.

The results reported by Travis et al clearly demonstrate the influence of radiation dose on the risk of breast cancer. Within the range of doses that have been used in the past to treat breast cancer, more radiation translates into a higher risk of developing breast cancer. This information, as well as data from earlier publications, supports the notion that “lower is better” as long as the radiation dose used augments the cure rate for HD. Although most data suggest a linear relationship between radiation dose and risk of breast cancer, the old hypothesis that the low nonlethal dose is most carcinogenic is still prevailing. The data presented by Travis et al argue against this notion.

An important issue not addressed by this study involves the volume of breast tissue exposed to radiation and its effect on the risk of breast cancer. During the last decade, reduction in field size has been the most important change in radiation therapy of HD. After chemotherapy, radiation therapy is now used as consolidation therapy and not as the primary treatment. Thus, the radiation fields currently used are targeting only the originally involved lymph node group (ie, involved-field radiation therapy). This strategy represents not only a shift in concept, but in reality is markedly reducing, and often eliminating, breast tissue exposure compared with the extended-field irradiation used in the past. At a minimum, extended-field radiation included the neck, supraclavicular, infraclavicular, axillary, mediastinal, and hilar regions in one wide field called the “mantle.” In the era during which radiotherapy included the mantle field, most breast exposure resulted from the radiation of the axillae (65% of tumors in this study developed in the outer part of the breast), and to a lesser extent from wide mediastinal and hilar irradiation.

Approximately two thirds of women with early-stage HD do not require radiation of the axillae, and additional protection to the upper and medial aspects of the breast could be provided by reducing field size further using careful computed tomography–based planning that usually allows for smaller mediastinal volumes, especially following chemotherapy. Prospective randomized studies have demonstrated that reducing volume and radiation dose after obtaining a complete remission with chemotherapy still retains the significant contribution of radiation therapy to the long-term control of HD. Reduction in the volume of exposed breast tissue, together with dose reduction (from more than 40 Gy to a dose in the range of 20-30 Gy), is likely to dramatically change the long-term risk profile of young male and female patients cured of HD. The findings of Travis et al on the radiation dose-risk effect are therefore encouraging.

Data on the effect of chemotherapy alone, and even more important, on the effect of chemotherapy on radiation-related risk of breast cancer, have been conflicting and much debated. The data reported by Travis et al soundly demonstrate that the use of alkylating agent–based chemotherapy alone reduced risk of breast cancer by 40%, and that when given with radiation, the risk was more than 4 times lower than if radiation was used alone. Ovarian irradiation had a similar protective effect. The data support the notion that hormonal stimulation is critical for radiation-induced breast carcinogenesis. Even stronger support for the relevance of hormonal stimulation is apparent in a separate analysis of the Dutch patient cohort by van Leeuwen et al. European patients probably had less exposure to hormone therapy than their North American counterparts, and the Dutch data demonstrate a clear relationship between early menopause and reduced risk of breast cancer after HD.

This finding is not only biologically exciting, but also may encourage interventions to reduce hormonal stimulation of breast tissue during and after treatment. Recent data in women at high risk for developing breast cancer demonstrated that tamoxifen reduced risk of breast cancer by 38%, and tamoxifen should possibly be considered for patients with HD who have been treated with radiation that resulted in breast exposure.

Rather than struggling with all of these risk modifiers, perhaps radiotherapy should simply be eliminated from the treatment regimen. Unfortunately, 2 recent prospective randomized studies suggest that this apparently easy approach is wrong. A study by the Children Cancer Group designed to compare involved-field, low-dose (21 Gy) radiotherapy to no radiation following a complete response to chemotherapy in HD was terminated early due to a high number of relapses in the group not receiving radiation, but still demonstrated that freedom from relapse was significantly greater in the group treated with radiation. For the same reason, an ongoing European Organisation for Research and Treatment of Cancer study (EORTC HD-9F) in patients with favorable early-stage HD terminated the group not receiving radiation (T. Girinsky, oral communication, and E. M. Noordijk, written communication, October 2002). The treatment groups receiving low-dose (20 Gy), involved-field radiotherapy for consolidation after complete remission, or full-dose (36 Gy) radiotherapy remain open for patient accrual. Exclusion of radiotherapy compromises the cure of HD.

The pendulum of therapy for HD that has swung from wide-field, full-dose radiation alone to full-dose chemotherapy and no radiation is likely to settle in the middle, providing a safer cure for Hodgkin disease by using brief chemotherapy and reduced radiation. The efficacy of this
strategy already has been demonstrated, but determination of potential long-term toxicity will require more time.

REFERENCES

Diet First, Then Medication for Hypercholesterolemia

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MANAGING DIET IS THE KEY TO TREATING ALL COMMON LIPID DISORDERS. Previous observations suggest that intensive dietary intervention can decrease serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels by approximately 30%. The findings of Jenkins and colleagues’ reported in this issue of THE JOURNAL indicate that intensive dietary therapy may be just as effective in reducing cholesterol levels as the starting dosage of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) drug.

In their preliminary investigation, Jenkins et al randomly assigned 55 healthy hyperlipidemic men and women to receive 1 of 3 treatments: a very low-saturated-fat diet based on whole-grain wheat cereals and low-fat dairy foods (control group); the same diet plus lovastatin, 20 mg/d (statin group); or a diet high in plant sterols, soy protein, viscous fibers, and almonds (dietary portfolio group). Based on data from the 46 patients who completed the 4-week study, the authors report that the statin and dietary portfolio treatment groups had approximately 30% reduction in LDL-C compared with an 8% reduction in the control group; they report roughly comparable results using an intention-to-treat analysis. These results are potentially important, given the expense, safety concerns, and intolerance related to statin use. Moreover, if confirmed in other rigorous investigations, these findings could have far-reaching implications for a large number of patients with dyslipidemia; those who are motivated to adopt prudent diets might achieve meaningful lipid reductions without pharmacotherapy.

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