

RISK OF LEUKEMIA AFTER CHEMOTHERAPY AND RADIATION TREATMENT FOR BREAST CANCER

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Abstract Background. Few studies have evaluated the late effects of adjuvant chemotherapy for breast cancer. Moreover, the relation between the risk of leukemia and the amount of drug given and the interaction of chemotherapy with radiotherapy have not been described in detail.

Methods. We conducted a case-control study in a cohort of 82,700 women given a diagnosis of breast cancer from 1973 to 1985 in five areas of the United States. Detailed information about therapy was obtained for 90 patients with leukemia and 264 matched controls. The dose of radiation to the active marrow was estimated from individual radiotherapy records (mean dose, 7.5 Gy).

Results. The risk of acute nonlymphocytic leukemia was significantly increased after regional radiotherapy alone (relative risk, 2.4), alkylating agents alone (relative

risk, 10.0), and combined radiation and drug therapy (relative risk, 17.4). Dose-dependent risks were observed after radiotherapy and treatment with melphalan and cyclophosphamide. Melphalan was 10 times more leukemogenic than cyclophosphamide (relative risk, 31.4 vs. 3.1). There was little increase in the risk associated with total cyclophosphamide doses of less than 20,000 mg.

Conclusions. Although leukemia occurs in few patients with breast cancer, significantly elevated risks were linked to treatments with regional radiation and alkylating agents. Melphalan is a more potent leukemogen than cyclophosphamide or radiotherapy. Low risks were associated with the levels of cyclophosphamide in common use today. Systemic drug therapy combined with radiotherapy that delivers high doses to the marrow appears to enhance the risk of leukemia. (N Engl J Med 1992;326:1745-51.)

SINCE the mid-1970s adjuvant chemotherapy has been widely used to treat breast cancer with regional lymph-node involvement.¹ More recently, systemic drug therapy has been given to women with localized disease, most of whom survive for many years without a recurrence of cancer.² Patients with breast cancer who are treated with chemotherapy, particularly regimens containing melphalan, are at increased risk of secondary leukemia.³⁻⁵ However, the risk associated with cyclophosphamide, the primary alkylating agent used today to treat breast cancer, has not been well explored. Moreover, there are few studies describing the dose-response relation of these drugs, their interaction with radiotherapy, and the effects on risk of age at the time of the diagnosis of breast cancer and timing of chemotherapy. Our study examines these questions in patients with breast cancer in five areas of the United States.

METHODS

Study Subjects

A case-control study was conducted in a cohort of 82,700 women with invasive breast cancer diagnosed from 1973 to 1985 who were reported to one of five population-based cancer registries (Connecticut, Iowa, and the metropolitan areas of Detroit, Atlanta [1975 to 1985], and Los Angeles). Because secondary leukemia does not develop until at least 1 to 2 years after therapy, only women who survived at least 18 months after the diagnosis of their breast cancer were eligible for study. Newly diagnosed cases of leukemia were

identified from registry files. Cases of chronic lymphocytic leukemia, which has not been related to radiation exposure or the use of cytotoxic drugs, were excluded. Death records were searched for patients with breast cancer whose underlying cause of death was severe anemia or another blood disorder. All suspected leukemic conditions were evaluated and reclassified with the use of reports and slides of peripheral-blood samples, bone marrow aspirates, and biopsy specimens. The 90 eligible case patients included 84 with leukemias and 6 with myelodysplastic syndrome. The leukemic conditions were classified as follows: 74 were acute nonlymphocytic leukemia, 3 were acute lymphocytic leukemia, 7 were chronic myelogenous leukemia, 5 were refractory anemia with excess of blasts, and 1 was acute myelofibrosis. The 20 women from Connecticut with leukemic conditions have been described previously.³ For each case patient, three control patients were selected by means of random sampling from the cohort of women with breast cancer, and they were matched to the case patient on the basis of age and year of diagnosis of the initial tumor (exact year, when possible), race or ethnic group, and length of follow-up, which had to be at least as long as the interval between the diagnosis of breast cancer and the onset of the leukemic condition. Three controls each were found for 84 case patients, and 2 controls each were found for the other 6 case patients.

Abstraction of Medical Records

Information about surgery, radiotherapy, chemotherapy, hormonal therapy, and demographic characteristics was abstracted from registry records, hospital charts, and oncology-clinic records. Because chemotherapy for breast cancer is frequently administered directly from physicians' offices, an attempt was made to contact all private physicians associated with the patients' treatment. Information regarding primary treatment was abstracted from the records kept by at least one of the patients' physicians (or clinics) for 90 percent of the case patients and 92 percent of the controls, and for subsequent courses of therapy for 85 percent of the case patients and 89 percent of the controls. For 3 percent each of the case patients and controls, yearly follow-up reports from the individual hospital tumor registries describing details of radiotherapy and chemotherapy were used to confirm the treatment information obtained from the medical records. Treatments given within one year before the diagnosis of leukemia (or an equivalent date for the controls) were considered unlikely to contribute to the development of a second cancer and were excluded from analyses.

Information on the cumulative dose of alkylating agents was

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