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Research paper

Cancer risk after adjuvant chemo- or chemohormonal therapy of breast cancer

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This study is based on 194 patients with primary breast cancer treated with adjuvant CNF combination chemotherapy, who were followed-up for the risk of subsequent neoplasms. During an average follow-up of 4.8 years, 16 cases of new cancers were detected. Nine non-breast cancers were observed versus 2.2 expected (standardized incidence ratio 4.2). Of the patients with subsequent malignancies, 88% had received antiestrogen (chemohormonal adjuvant therapy); the percentage among all patients was 25%. We conclude that the benefit derived from adjuvant therapy of breast cancer may be reduced because of an increased risk of subsequent cancers. [© 1998 Rapid Science Ltd.]

Key words: Adjuvant therapy, breast cancer, cancer risk, chemotherapy, secondary leukemia.

Introduction

Adjuvant therapy for breast cancer is recommended as standard treatment for node-positive and even for some node-negative patients. Adjuvant polychemotherapy has been shown to decrease the risk of death due to the primary cancer, especially in premenopausal women.[1] Survival for women with breast cancer has improved significantly within recent decades,[2] so that the occurrence of late effects of adjuvant treatment has gained more clinical importance.[3] The increased risk for second primary cancers after adjuvant therapy of breast cancer has been recognized in many studies.[4–15] This risk can be due to chemo-, endocrine or radiation therapy.

A combination of CNF [cyclophosphamide, mitoxantrone (Novantrone®) and 5-fluorouracil] has been proven to be effective in the treatment of metastatic breast carcinoma.[14] The CNF combination has been found suitable as adjuvant treatment and the acute side effects have been reported to be tolerable.[15]

The aim of this study was to describe the risk for second primary neoplasms in Finnish CNF-treated patients with early breast cancer. Special attention was paid to those cancers with an *a priori* suspected association with adjuvant therapy of breast cancer, i.e. leukemia, cancer of the endometrium and bladder, and bone and soft tissue sarcomas.

Materials and methods

From June 1986 to January 1994, adjuvant CNF-based chemotherapy was administered to 194 female patients who had operable breast cancer. Starting in February 1990, the first two cycles were replaced with a CMF regimen (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 500 mg/m^2). This was done to allow chemotherapy to be started simultaneously with postoperative radiation therapy, thus shortening the overall treatment duration, and to decrease the assumed additive risk of cardiotoxicity. In addition to chemotherapy, tamoxifen was given as adjuvant hormonal therapy to 48 patients (25% of the patients). Adjuvant postoperative radiotherapy was administered to all the patients at a daily dose of 2 Gy to a total dose of 50 Gy. The patients were followed-up every 3 months for 2 years and once or twice a year thereafter.

In addition to ordinary follow-up, the subsequent cancers and deaths were recorded through the files of the Finnish Cancer Registry using the personal identification number as a key. Follow-up for cancer started on the date the adjuvant CNF treatment was begun and ended at death or on 31 December 1995, whichever occurred first. The numbers of observed cases and person-years at risk were counted by 5-year age groups. The expected numbers of cases for all cancers and for specific cancer types were calculated

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by multiplying the number of person-years in each age group by the corresponding average cancer incidence in the female population in Eastern Finland during the period of observation. Further division was made by the time elapsed since CNF treatment. The specific cancer types selected *a priori* for the analysis included those cancer sites with known or suspected exceptional risk in earlier studies, as well as other common cancer types, to give a description of cancer morbidity among Finnish breast cancer patients treated with adjuvant chemotherapy. Cancers—both observed and expected—occurring in the breasts were excluded from the analysis.

To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. Statistical significance was tested by the Mantel-Haenszel χ^2-test, assuming that the number of observed cases followed a Poisson distribution.

Table 1. SIRs of secondary neoplasms after CNF/CMF chemotherapy

Neoplasm	Obs	Exp	SIR	95% CI
All neoplasms	16	3.7	4.3	2.5–7.0
Breast	7	1.5	4.5	1.8–9.4
All neoplasms, breast excluded	9	2.2	4.2	1.9–7.9
uterine corpus	2	0.2	8.2	1.0–30
leukemia	2	0.1	38	4.6–135
other *a priori* site[a]	0	0.1	0	0.0–53
other	5	1.8	2.8	0.9–6.5

Exp = expected number of new cases in the cohort; Obs = observed number of new cases in the cohort; CI = confidence interval (of the SIR).
[a]Bladder, bone soft tissue.

Results

There were 194 women under follow-up in the cohort. The number of person-years was 922, with a mean length of follow-up of 4.8 years.

During the follow-up, 16 cases of new cancer were diagnosed in the cohort; the expected number was 3.7 (Table 1). Seven of the new cancers were breast neoplasms and were excluded (SIR for breast cancer 4.5, 95% CI: 1.8–9.4). In the remaining sites there were 9 cases versus 2.2 expected (Table 1); this increase was statistically significant ($p < 0.001$). The new cancers were as follows: one esophageal carcinoma, two carcinomas of the uterine corpus, one papillary carcinoma of the ovary, one meningioma, two leukemias (FAB M3 and M4e) and two lymphomas. In one patient both a cancer of the uterine corpus and ovarian cancer were detected. The SIR for leukemia (38, 95% CI: 4.6–135) was significantly elevated.

The adjuvant therapies (chemotherapy, radiotherapy and hormonal therapy) together with the period between the onset of adjuvant chemotherapy and the diagnosis of the second primary tumor are summarized for each patient in Table 2.

Discussion

Combination therapy of breast cancer has been adopted widely.[1] When administering medical treatment and radiotherapy as adjuvant therapy, the benefits and risks related to therapy must be carefully taken into account. The risk of secondary cancers is

Table 2. Characteristics of the patients with a secondary malignancy other than breast cancer

Patient	Age	Adjuvant therapy	Latency (months)	Neoplasm	Therapy, follow-up status
1	54	CNF × 4/CMF × 2, RT	39	Hodgkin's lymphoma	RT→CR at 24 months, alive
2	46	CNF × 4/CMF × 2, RT, TAM	25	uterine corpus	operation + intracavitary RT→CR at 25 months, alive
3	65	CNF × 4, RT, TAM	45	esophagus	NT→died after 2 months
4	42	CNF × 6, RT, TAM	50	NHL (thyroid)	CHOP × 10→CR at 43 months, alive
5	61	CNF × 6, RT, TAM	63	uterine corpus	operation + intracavitary RT→carcinoma of ovary
			75	ovary	CEF × 4, Cis-C→PR in 3 months, died after 10 months
6	66	CNF × 5, RT, TAM	30	AML (M3)	died within 5 days in sepsis and MI
7	51	CNF × 6, TAM, RT	19	AML (M4e)	alive at 34 months (second relapse)
8	52	CNF × 4, CMF × 2, RT	18	meningioma	operation→CR in 28 months, alive

Latency = time between the onset of adjuvant treatment and subsequent cancer; Therapy = therapy for subsequent cancer; Age = age in years at the onset of adjuvant therapy; C = cyclophosphamide; N = mitoxantrone; F = 5-fluorouracil; M = methotrexate; Cis = cisplatin; CHOP = cyclophosphamide + adriamycin + vincristine + prednisolone; RT = radiotherapy (50 Gy for breast cancer); CR = no evidence of disease; TAM = tamoxifen; NT = no treatment; MI = myocardial infarction.

one of the most important risk factors to be considered.

Radiation has been shown to induce leukemias, e.g. after the A-bomb, with the highest incidence at 5–7 years after exposure.[16] Postoperative irradiation given to a limited area has not significantly influenced the risk for second malignancies. It is generally accepted that the risk of secondary solid tumors is increased only after 10 years after the radiotherapy. The most common second malignancy is contralateral breast cancer, but less than 3% of these tumors can be attributed to radiation.[17] In this study, the patient with esophageal carcinoma had the tumor in the area previously irradiated. The latency period after radiation was rather short, 45 months, and esophageal cancer is not considered to be radiation related.[18]

During a median follow-up of 12 years, Valagussa *et al.*[4] found a relative risk of 1.29 for second malignancies in CMF-treated patients when compared to the general female population. They reported a relative risk of 2.3 for acute non-lymphocytic leukemia. The risk of leukemia was associated with the cumulative dose of cyclophosphamide. Breast irradiation did not enhance this risk.

In a study by Tallman *et al.*,[5] a total of 2638 patients from six clinical trials of adjuvant chemotherapy were followed-up with a mean of 7.3 years. The protocols consisted of CMF-based chemotherapy with or without tamoxifen or prednisolone. The risk of AML or myelodysplastic syndrome in the cohort was not much higher than in the general population.

In some studies dealing with adjuvant chemotherapy, the addition of tamoxifen to CMF has been considered to exert an overall protective effect. In a study by Rubagotti *et al.*[6] of a total of 1286 patients receiving CMF, tamoxifen or the combination. CMF-treated patients showed an approximately 2-fold risk of secondary tumors as compared to the general population. A reduction in the total cancer risk was noticed in patients receiving tamoxifen. Patients treated with chemoendocrine adjuvant therapy, and those without treatment, showed a risk comparable to that of the general population. In the study by Arriagada and Rutqvist,[7] which included 1113 patients with a follow-up of 10 years, the estimated rate of new malignancies was significantly lower in patients treated with chemotherapy (1%) than in patients treated with radiation therapy (6%). The matched breast cancer patients without either treatment had a 5% rate of new malignancies. They concluded that adjuvant chemotherapy (CMF or LMF) may protect against the formation of new primary tumors. No cases of leukemia were detected.

The use of adjuvant tamoxifen has been associated with subsequent carcinoma of the uterine corpus in many studies. As stated in a thorough review article by Assikis and associates,[8] there is a definitive 2- to 3-fold increase in the risk of developing an endometrial cancer. We saw two cases, 10 times the expected number.

The alkylating agents such as cyclophosphamide have been implicated as causing leukemia, both as single agents and in combinations.[9] Evolution to overt acute myelocytic leukemia usually occurs after a latent period of 2–10 years. In many cases a period of pancytopenia may be diagnosed before the evolvement of leukemia. FAB types M1, M2 and M6 are the usual types of leukemia diagnosed after the administration of alkylating agents.[17]

Leukemia may be underdiagnosed, especially if the onset of leukemia occurs after the detection of breast cancer metastases. Signs and symptoms of leukemia or myelodysplastic syndrome can erroneously be attributed to progression of breast cancer. Fisher *et al.*[10] detected 16 of 43 leukemias or myeloproliferative syndromes after a relapse of breast cancer or the appearance of a secondary tumor. Treatment given for breast cancer relapse may also be responsible for leukemias later in the life of breast cancer patients. It is difficult to choose a pertinent cohort for comparison of the risk. Due to keen follow-up studies (laboratory tests, mammograms, etc.), a higher than usual detection rate of cancer may be possible, when compared with the general population. However, most of the cancers diagnosed in our cohort were detected on the basis of symptoms.

Bladder cancer has been associated with treatment with cyclophosphamide.[19] In our material, however, no cases of bladder cancer were diagnosed, which may be due to the short follow-up.

Lymphomas are not usually considered to be treatment-related tumors after chemo- or radiation therapy. Lavey *et al.*[11] and Herring *et al.*[12] did not report any lymphomas in their cohorts of 1081 and 797 breast cancer patients. Schwartz *et al.*[13] performed a population-based analysis of 17 944 breast cancer patients and the SIR of subsequent non-Hodgkin's lymphoma was 0.82 (95% CI: 0.47–1.33). Our study is the first report showing a significantly increased risk of secondary lymphoma (2 observed cases versus 0.1 expected) after curative treatment of breast cancer.

Conclusions

There is a certain risk of leukemia after chemotherapy. Therefore, every effort has to be made to find effective

adjuvant therapies which are less carcinogenic than those currently used. An increase in the risk of cancer was detected after the administration of CNF-based adjuvant breast cancer therapy. Further collection of data concerning therapeutic results and adverse effects of adjuvant chemotherapy seems warranted.

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