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CLINICAL INVESTIGATION **Breast**

CONCURRENT CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLUOROURACIL CHEMOTHERAPY AND RADIOTHERAPY FOR EARLY BREAST CARCINOMA

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Purpose: The optimal sequencing of adjuvant chemotherapy (CT) and radiation therapy (RT) in patients with early-stage breast cancer remains unclear.

Patients and Methods: We retrospectively compared 485 patients treated with conservative breast surgery and postoperative whole-breast RT and six courses of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) with 300 patients who received postoperative CMF only and with 509 patients treated with postoperative whole-breast RT only. The mean radiation dose delivered was 50 Gy (range, 46–52 Gy) with standard fractionation. The boost dose was 6–16 Gy according to resection margins and at the discretion of the radiation oncologist. Acute and late RT toxicity were scored using respectively the Radiation Therapy Oncology Group and the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale.

Results: A slightly higher Grade 2 acute skin toxicity was recorded in the concurrent group (21.2% vs. 11.2% of the RT only group, $p < 0.0001$). RT was interrupted more frequently in the CMF/RT group respective to the RT group (8.5% vs. 4.1%; $p = 0.006$). There was no difference in late toxicity between the two groups. All patients in the concurrent group successfully received the planned dose of RT and CT. Local recurrence rate was 7.6% in CT/RT group and 9.8% in RT group; this difference was not statistically significant at univariate analysis (log-rank test $p = 0.98$). However, at multivariate analysis adjusted also for pathological tumor, pathological nodes, and age, the CT/RT group showed a statistically lower rate of local recurrence ($p = 0.04$).

Conclusions: Whole-breast RT and concurrent CMF are a safe adjuvant treatment in terms of toxicity. © **2008 Elsevier Inc.**

Whole breast radiotherapy, CMF, Combined adjuvant treatment.

INTRODUCTION

Concurrent delivery of radiotherapy (RT) and chemotherapy (CT) is an alternative to sequential regimens in the adjuvant treatment of patients with breast carcinoma. Concurrent treatment allows both therapies to be given without delay, potentially improving their efficacy. Multiple studies have suggested that delaying radiation after surgery can result in an increased risk of local disease recurrence (1–4). However, delaying CT after the completion of radiation may increase the risk of distant metastases (5). Moreover concurrent administration of systemic therapy may potentially enhance the biological efficacy of RT, with synergistic effects on tumor control (6) but increase the toxicity of RT (7–8).

At the University of Florence, our policy is to deliver concurrent adjuvant CMF and RT in patients with early breast carcinoma because we believe that the concurrent treatment does not increase acute and late toxicity.

The aim of this study was to evaluate whether concurrent sequencing of standard doses of both CMF and radiation therapy influences the ability to deliver optimal doses of both treatment modalities and therefore has an impact on local recurrence.

PATIENTS AND METHODS

From January 1980 to December 2001, 485 patients with early breast cancer underwent concurrent adjuvant CT and RT at the University of Florence. In the current analysis, we included patients without clinical and radiological evidence of local or distant recurrence after breast-conserving surgery at the time of the first evaluation in our radiotherapy unit. None of the patients had prior

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malignant disease. The mean age of the patient population was 48.9 years (± 7.7 years; range, 35–65).

According to the protocol followed at our institute, all patients received RT to the whole breast only. All patients were treated with external beam RT using tangential fields of 6-MV photons. The mean delivered dose was 50 Gy (range, 46–52 Gy), in 2-Gy daily fractions. The dose was prescribed at the isocenter, according to the International Commission on Radiation Units and Measurements Report 50 guidelines. The tumor bed boost was given by electrons. At the discretion of the radiation oncologist, the total boost dose (in 2-Gy daily fractions) ranged from 6 to 10 Gy for patients with tumor-free surgical margins and between 14 and 16 Gy for patients with positive margins.

Computed tomography consisted of intravenous CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) on days 1 and 8, repeated every 28 for a total of six courses.

These patients were retrospectively compared with 300 patients who received CMF only (mean age, 46.7 ± 6.3 years; range, 35–65 years) and to 509 patients treated with whole-breast RT only (mean age, 52.5 ± 7.7 years; range, 35–65 years).

All the patients belonging to the group treated with CMF alone underwent mastectomy, and it was decided that including RT as a part of their adjuvant treatment was not indicated.

The main characteristics of the three groups of patients are reported in Table 1. The mean follow-up was 7.1 years (range, 0.6–23 years) for the CT/RT group, 8.5 years (range, 0.6–25 years) for the CHT group and 10.2 years (range, 0.6–23 years) for RT group. All the groups were treated in the same period from January 1980 to December 2001.

We evaluated whether concurrent CMF and RT may result in higher acute skin toxicity and thus lead to an increase in local recurrence rates due to a higher number of interruptions during RT. Acute radiation skin toxicity was scored weekly during radiation therapy according to the Radiation Therapy Oncology Group scale (8, 9). To assess late toxicity we used the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale (10, 11) scale.

Statistical analysis

Simple cross-tabulations (with two-tailed Fisher exact test or chi-square for trend, as appropriate) were used to compare selected parameters between study groups. For the survival analysis, we considered the date of surgery as the start of observation. Local disease-free survival time (breast relapse) was calculated from the date of surgery to the date of relapse occurrence. The crude probability of local relapse was estimated by using the Kaplan-Meier method, and differences between patient groups were assessed by the log-rank test. Survival comparisons were carried out using Cox proportional hazard regression models. A regression model with stepwise selection was performed to identify the major significant local relapse predictors.

Statistical results were considered significant at a p value <0.05. All statistical tests were performed with SAS software.

RESULTS

Data regarding acute skin toxicity is shown in Table 2. A significant statistical difference in the distribution of RT toxicity between the two groups emerged ($p < 0.0001$). Particularly, a slightly higher grade 2 toxicity was recorded in the concurrent group (21.2% *vs* 11.2% of the RT only group).

RT was stopped more frequently in the CMF/RT group respective to patients who underwent whole-breast RT only (8.5% vs. 4.1%; Table 3). This difference was statistically significant ($p = 0.006$). In a logistic model with stepwise selection (with RT stop as dependent variable), no parameter

Table 1. Distribution of 1,294 breast cancer cases according to selected clinicopathologic characteristics in the three study groups

Clinicopathologic characteristic	CT/RT	CT	RT
n	485	300	509
SD (range)	48.9 ± 7.7 (35–65)	46.7 ± 6.3 (35–65)	52.5 ± 7.7 (35–65)
Age groups (years), *n* (%)			
≤ 50	292 (60.2)	213 (71.0)	189 (37.1)
>50	193 (39.8)	87 (29.0)	320 (62.9)
pT, *n* (%)			
1	328 (67.6)	63 (21.0)	365 (71.7)
2	144 (29.7)	186 (62.0)	116 (22.8)
3	-	33 (11.0)	24 (4.7)
4	13 (2.7)	18 (6.0)	4 (0.8)
Mean nodes removed ± SD (range)	16.7 ± 8.7 (0–52)	19.5 ± 9.4 (0–53)	16.0 ± 9.2 (0–46)
Positive nodes, *n* (%)			
None	205 (42.3)	40 (13.3)	438 (86.1)
1–3	248 (51.1)	162 (54.0)	54 (10.6)
>3	32 (6.6)	98 (32.7)	17 (3.3)
Tamoxifen use,* *n* (%)			
No	318 (65.6)	267 (89.3)	330 (65.6)
Yes	167 (34.4)	32 (10.7)	173 (34.4)
Locoregional relapse occurrence, *n* (%)			
No	448 (92.4)	221 (73.7)	459 (90.2)
Yes	37 (7.6)	79 (26.3)	50 (9.8)
Distant metastases, *n* (%)			
No	422 (87.0)	157 (52.3)	443 (87.0)
Yes	63 (13.0)	143 (47.7)	66 (13.0)

Abbreviations: CT = chemotherapy; RT = radiotherapy; pT = pathological tumor.
* Some data are not available.