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A preliminary report of a pilot randomized trial comparing cyclophosphamide, methotrexate and 5-fluorouracil with cyclophosphamide, mitoxantrone and 5-fluorouracil in the adjuvant therapy of stage II breast cancer with four or more positive axillary nodes

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Thirty-eight patients with stage II breast cancer with four or more positive axillary lymph nodes were randomized to receive CMF (cyclophosphamide, methotrexate and 5-fluorouracil, every 3 weeks) or CXF (cyclophosphamide, mitoxantrone and 5-fluorouracil, every 3 weeks). Pretreatment characteristics were similar for both groups. The actuarial 5 year disease-free survival (DFS) was 36% for the CMF group and 23% for the CXF group. The actuarial 5 year survival was 60% for the CMF arm and 66% for the CXF arm. These differences were not statistically significant. Partial alopecia was observed in 42% of patients in the CMF arm and in 100% of those receiving CXF ($p = 0.0002$). No episodes of leucopenic fever were observed in patients receiving CMF, while they were present in 53% of patients treated with CXF ($p = 0.0006$). No stomatitis occurred in the CMF group, but it was observed in 90% of patients who received CXF ($p < 0.0001$). Treatment with CXF had to be discontinued in two patients because of toxicity. In this small group of patients with poor prognosis, it seems that CXF at the doses given here is more toxic but not more effective than CMF, as represented by a similar DFS and survival.

Key words: Combination chemotherapy, mitoxantrone, stage II breast cancer.

Introduction

Combination chemotherapy has been the primary modality for the treatment of metastatic breast cancer. Since 1969, when Cooper *et al.*[1] reported the results of the combination of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone (CMFVP), numerous other regimens have been evaluated. One of them, the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF), has become widely used in the treatment of metastatic disease,[2–4] and for the adjuvant therapy of primary breast cancer.[5,6]

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Doxorubicin has generally been considered to be one of the most active single drugs in the treatment of breast cancer.[7] When methotrexate was substituted by doxorubicin, another combination was produced: CAF (cyclophosphamide, doxorubicin and 5-fluorouracil). Most clinical studies comparing CAF versus CMF in the treatment of metastatic breast cancer have demonstrated that CAF is more therapeutically effective, although no significant differences in survival were observed when comparing both combinations.[8,9]

Mitoxantrone, a dihydroxy-anthracenedione, is a synthetic DNA intercalcating agent, without the aminosugar of doxorubicin. It was predicted that the antineoplastic activity will be retained and cardiotoxicity will be reduced.[10] Mitoxantrone as a single agent has proven to be an effective treatment modality for metastatic breast cancer.[11–14]

A large randomized clinical trial comparing mitoxantrone with doxorubicin was reported by Henderson *et al.*[10] In this study, the authors demonstrated a comparable therapeutic effectiveness, and also that mitoxantrone had a more safety profile in terms of nausea, vomiting, stomatitis, mucositis, alopecia and, more particularly, cardiotoxicity than doxorubicin. These observations led to the substitution of mitoxantrone for doxorubicin in the CAF regimen.

The first study of cyclophosphamide, mitoxantrone and 5-fluorouracil (CXF) in the treatment of advanced breast cancer was reported by Holmes *et al.*[15]. In this study, the overall response rate was 68%, with a median duration of 7 months.

Based upon these observations, it seemed reasonable to evaluate the efficacy of CXF, especially after the encouraging reports of Fisher *et al.*[16] when adding doxorubicin to the L-PAM regimen.

Materials and methods

Between September 1986 and May 1990, 38 patients suffering from stage II breast cancer, with four or more involved axillary lymph nodes, were randomized to receive CMF or CXF. Patients were planned to receive six courses of either regimen.

Patient characteristics are shown in Table 1. Number of patients, age, number of involved/examined axillary lymph nodes and median number of days from diagnosis to onset of chemotherapy were similar for both groups. There was a slight predominance of premenopausal patients in the CXF group.

Chemotherapy was administered as follows. CMF: cyclophosphamide, i.v., 600 mg/m^2; methotrexate, i.v., 40 mg/m^2; and 5-fluorouracil, i.v., 600 mg/m^2, every 3 weeks. CXF: cyclophosphamide, i.v., 600 mg/m^2; mitoxantrone, i.v., 12 mg/m^2; and 5-fluorouracil, i.v., 600 mg/m^2, every 3 weeks.

Cardiotoxicity was monitored with serial physical examinations, ECGs and MUGA scans; these were required before treatment for all patients, and every two courses for patients randomized for CXF.

Analysis of survival was calculated according to the life-table method.[17] The generalized Wilcoxon test was utilized to evaluate differences between subgroups.[18] The p value was a two-tailed test.

Table 1. Patient characteristics

	CMF	CXF
No. of patients	19	19
Median age (range)	46 (34–59)	41 (25–64)
Median no. of involved nodes (range)	6 (4–40)	7 (4–15)
Median no. of examined nodes (range)	20 (12–43)	17 (10–42)
Median days to chemotherapy (range)	28 (9–44)	31 (11–49)
Menstrual status		
premenopausal	11 (58%)	15 (79%)
postmenopausal	8 (42%)	4 (21%)
Estrogen receptor status		
positive	6 (31.5%)	9 (47%)
negative	7 (36%)	7 (37%)
unknown	6 (31.5%)	3 (16%)
Median follow-up months (range)	42 (15–63)	44 (15–61)

Results

The actuarial 5 year disease-free survival (DFS) for all patients was 27%. The actuarial 5 year DFS was 36% for the CMF group and 23% for the CXF group ($p = 0.50$). The actuarial 5 year survival for all patients was 63%. The actuarial 5 year survival was 60% for the CMF group and 66% for the CXF group ($p = 0.31$).

Toxicity of both treatment groups is shown in Table 2. There were no significant differences in the nadir of leucocytes or platelets in both treatment groups, although in patients receiving CXF there were 10 episodes of leucopenic fever (53%) with uneventful recovery (WHO grade 3; $p = 0.0006$). Partial alopecia (WHO grade 2) was observed in eight of 19 patients (42%) in the CMF arm and in all 19 patients (100%) in the CXF arm ($p = 0.0002$). No stomatitis occurred in the CMF group, but WHO grade 2 stomatitis was observed in 17 of 19 patients (90%) who received CXF ($p < 0.0001$). Treatment with CXF had to be discontinued in two patients who experienced cardiotoxicity (cumulative doses of mitoxantrone of 80 and 110 mg, respectively), as demonstrated by MUGA scan (reduction of 18 and 20%, respectively, although no clinical manifestations of cardiotoxicity were observed).

Table 2. Side-effects of CMF and CXF regimens

	CMF	CXF	p value
Median nadir WBC/mm^3 (range)	2700 (1000–5800)	800 (400–3700)	NS
Episodes of leucopenic fever (WHO grade 3)	0/19	10/19	0.0006
Median nadir PLT/mm^3 (range)	144 000 (88 000–229 000)	118 000 (74 000–219 000)	NS
Partial alopecia (WHO grade 2)	8/19	19/19	0.0002
Stomatitis (WHO grade 2)	0/19	17/19	<0.0001
Treatment discontinued for toxicity	0/19	2/19	NS

Discussion

The results presented herein showed that no statistically significant differences in DFS or survival between CMF and CXF were observed in patients with stage II breast cancer with four or more involved axillary nodes.

In operable breast cancer, the probability of relapse and survival are related to the pathological status of the axillary lymph nodes and the degree of nodal involvement remains the most important indicator of treatment outcome.[19] Moreover, the National Surgical Adjuvant Breast and Bowel Project and the Istituto Nazionale Tumori in Milan[6,20] have stressed the need for a further subdivision of patients with more than three involved axillary nodes. As a matter of fact, it has been reported that the DFS and survival of patients with more than 10 involved axillary nodes are very poor, regardless of the administered therapy.[21] As a consequence of this observation, the Consensus Development Conference[22] established four nodal categories: negative, one to three, four to nine, and more than 10 positive nodes. According to these categories, our patients represented from the beginning a group with poor prognosis, in view of the low rates of DFS and survival.

However, because of the small number of patients in each group, the results of our pilot study should be interpreted with caution.

Since the time this pilot study was closed for accrual, the Israel Cooperative Oncology Group (ICOG) has designed a multicenter study comparing the effectiveness of CMF versus CXF in patients with positive nodes, i.e. patients are accrued starting with one involved node. Until June 1992, 200 patients were accrued, but no results of this trial are available as yet.

There are no reports of the CXF regimen given in the adjuvant setting, except for a report by Bonadonna *et al.*,[23] in which 165 women with primary breast cancer were neoadjuvantly treated with CMF, CAF, FEC (E = epirubicin) or FNC (N-mitoxantrone). In this trial, patients were evaluated for response to chemotherapy in order to avoid mastectomy and treated thereafter in a conservative fashion, although no data was reported on which of these combinations seemed to be more effective.

In conclusion, in this small group of patients with poor prognosis, it seems that CXF at the doses administered here may be more toxic but not more effective than CMF, as represented by a similar DFS and survival. Further patient accrual with one to three positive axillary nodes is needed to evaluate CXF chemotherapy in this relatively more benign subset of patients. Dose adjustments of CXF should also be considered.

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