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CNF combination as adjuvant treatment in breast cancer patients is well tolerated

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In this study 194 women with breast cancer received adjuvant CNF combination therapy (cyclophosphamide, mitoxantrone and 5-fluorouracil). The side effects and acute toxicity of the regimen were recorded. Although myelosuppression is the dose-limiting factor of the CNF regimen, it was well tolerated and side effects were limited. This regimen induced no cardiotoxicity or irreversible alopecia. It is concluded that CNF is suitable as adjuvant chemotherapy for breast cancer patients.

Key words: Adjuvant, breast, chemotherapy, cyclophosphamide, fluorouracil, neoplasm, mitoxantrone, side effects.

Introduction

The benefits of adjuvant combination chemotherapy in premenopausal breast cancer patients have been demonstrated in many clinical trials.[1] Adjuvant therapy, either chemotherapy for premenopausal or tamoxifen for postmenopausal women, is recommended as standard treatment for node-positive women.[2] A combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) is probably the most commonly used adjuvant therapy.[3] In the treatment of metastatic breast cancer, combinations containing doxorubicin have been considered to be the most effective.[3] However, in some trials no statistically significant differences between anthracycline-containing combinations and others have been demonstrated.[4,5]

Mitoxantrone (Novantrone®) is an intercalating agent of milder toxicity than doxorubicin.[6] A combination of cyclophosphamide, mitoxantrone and 5-fluorouracil (CNF or CXF) has been shown to be effective in advanced breast cancer.[7,8] Based upon these results in advanced breast cancer, we introduced the CNF combination as adjuvant chemotherapy and aimed at increasing the efficacy of adjuvant therapy. This paper summarizes our experience of CNF as an adjuvant chemotherapy in breast cancer with special reference to toxicity, side effects and tolerability.

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Materials and methods

Women with breast cancer but no history of any other cancer apart from non-melanoma skin cancer or *in situ* cervical cancer were eligible for enrollment in this study. Patients receiving CNF as neoadjuvant therapy were excluded. From June 1986 to January 1994, 194 consecutive patients were administered CNF (cyclophosphamide 500 mg/m^2, mitoxantrone 10 mg/m^2 and 5-fluorouracil 500 mg/m^2 every 4 weeks) following the completion of postoperative radiotherapy. To allow chemotherapy to be started simultaneously with postoperative radiation therapy and thus shorten the overall treatment duration, we replaced the first two cycles with a CMF regimen (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 500 mg/m^2) since February 1990. Because of possible additive cardiotoxicity, radiation therapy and mitoxantrone were not given simultaneously.

Patient characteristics are shown in Table 1. The median age was 47 years (range 27–68 years). Most patients (90%) had undergone radical mastectomy. Twenty patients (10%) had been subjected to quandrantectomy or lumpectomy. Postoperative radiotherapy was administered to 191 patients. Antiestrogen (tamoxifen) was added to adjuvant chemotherapy to 48 patients (25%). Nine patients had been surgically treated following a locoregional relapse.

Before therapy, the patients were subjected to physical examination, radionuclide bone scan, liver ultrasound scanning, chest X-ray and laboratory examinations which included blood count, serum creatinine and alkaline phosphatase levels. The peripheral blood count was determined before each

Table 1. Characteristics of the patients

Characteristic	No. of patients (%)
Stage (according to TNM classification)	
1	2 (1)
2A	62 (31)
2B	75 (39)
3A	41 (21)
3B	5 (3)
locoreg relapse	9 (5)
Histopathological grade	
1	13 (7)
2	84 (43)
3	69 (36)
unknown	28 (14)
Menopausal status	
premenopausal	125 (64)
postmenopausal	35 (18)
unknown	34 (18)

cycle. The toxicity and side effects recorded in the patients' case histories were reported in accordance with the WHO criteria.[9] After completing the adjuvant treatment, patients were followed up every 3 months during the first 2 years (clinical status, routine laboratory tests and chest X-rays) and then once or twice a year.

Results

The numbers of CNF and CMF cycles were 901 and 228, respectively. Side effects and acute toxicities in accordance with WHO criteria are listed in Table 2. Fatty liver was detected in three (2%) patients after adjuvant chemotherapy. Complaints of headache and paresthesias were made by 11 patients (6%) and 14 patients (7%), respectively. Fifteen (8%) women suffered from dysuric symptoms or urinary tract infection; 21 (10%) patients complained of arthralgias. Amenorrhea was induced in 59 (47%) and menopausal symptoms in 27 (22%) of 125 premenopausal women. During the 901 CNF cycles, grade 3 leukopenia was detected during 87 cycles (10%) in 59 (10%) patients and grade 4 leukopenia during 12 cycles (1%) in nine (5%) of the 194 patients. Dose reductions were made because of leukopenic episodes in 35 patients. Conjunctivitis was seen in nine patients (5%). No signs of cardiotoxicity or therapy-related deaths were recorded.

Table 2. Acute toxicity of CNF regimen in 194 patients according to WHO classification

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	21 (11)[a]	2 (1)	-	
Leukopenia	48 (25)	51 (26)	59 (30)	9 (5)
Thrombocytopenia	5 (3)			
Nausea and vomiting	76 (40)	50 (26)	2 (1)	1 (1)
Alopecia	27 (14)	9 (5)	3 (2)	
Stomatitis	7 (4)	7 (4)		
Allergic reaction	1 (1)	1 (1)		
Abdominal pain	7 (4)	1 (1)		
Constipation	3 (6)	1 (1)		
Diarrhea	6 (3)	6 (3)	1 (1)	
Skin reaction	14 (7)	2 (1)	1 (1)	

[a]No. of patients (%).

The treatment of 21 patients was discontinued; in nine of these patients the reason was subjective side effects. Leukopenic episodes of fever were recorded in five patients. Three breast cancers relapsed during adjuvant chemotherapy.

Serum alkaline phosphatase levels were high in four patients (WHO grade 1) before chemotherapy. After adjuvant therapy grade 1 elevations were seen in seven patients. One of the patients had a fatty liver, as diagnosed by ultrasonography.

No elevations in serum creatinine levels were seen during adjuvant chemotherapy. All values before and after chemotherapy were within the normal range (below 95 mmol/l).

Sixty-four of our patients relapsed during follow-up. The commonest sites of relapse were bone (27 patients), lung (19 patients) and locoregional sites (18 patients). Three patients (2%) died of causes other than breast cancer. One patient gave birth to a healthy baby 3 years after exposure to the CNF regimen.

Discussion

Isaeson *et al.*[10] reported a pilot randomized trial comparing CMF and CNF as adjuvants. No statistically significant differences in survival between the two regimens were recorded. Cardiotoxicity was found in two patients who had no clinical manifestations. The incidence of partial alopecia (100%) and stomatitis (90%) (both WHO grade 2) far exceeded the rates observed by us. In their study, CNF was more toxic than CMF.

Metastases in our patients were most frequent in bone, lung and locoregional sites. These findings are similar to those in a report covering over 2000 recurrences.[11]

When chemotherapy is used as adjuvant treatment in patients with breast cancer, the benefits and side effects of therapy need to be evaluated with the

utmost care. Although doxorubicin-containing regimens seem the most effective against advanced breast cancer,[3] the side effects of the regimen are considerable.[12] Alopecia is usually total and long-term cardiotoxicity may be significant. By substituting the anthracenedione mitoxantrone for doxorubicin, we obtained a tolerable range of side effects and toxicity.

Myelosuppression was the dose-limiting factor in our study. Adjuvant treatment was discontinued in 21 patients because of side effects. Five patients experienced febrile leukopenic episodes during treatment. Generally, toxicity was tolerable and no therapy-related deaths were observed.

Conclusions

Long-term follow-up is required to determine survival rates and to identify delayed toxic side effects. Because CNF is well tolerated, and there may be an advantage in replacing the anthracenedione mitoxantrone for methorexate, a large prospective randomized trial is recommended to compare CNF with CMF as an adjuvant chemotherapy. We conclude that CNF is a suitable adjuvant chemotherapy regimen with low toxicity.

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