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Palliative chemotherapy with CMF after the same adjuvant regimen for breast cancer

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Abstract

Background: The results of palliative chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in patients with advanced breast cancer who received adjuvant therapy with the same regimen were investigated.

Results: Of 47 patients, 14 (30%) achieved an objective remission (median duration 9.5, range 5–21 months) and 8 (17%) stabilisation of disease (median duration 6, range 3–17 months). Objective remissions were observed in premenopausal as well as in postmenopausal women, in patients with all categories of dominant localisation of disease and regardless of the oestradiol receptor status of the primary tumour or eventual previous endocrine therapy. One of 4 and 13 of 43 patients who started palliative chemotherapy within or later than 12 months after the last adjuvant course obtained an objective remission. The median survival time from start of therapy of all treated patients was 12 (range 1–40) months. Patients with an objective remission or stable disease and patients with progressive disease had a median survival time of 20 (range 6–40) and 6 (range 1–35) months respectively ($p < 0.0001$).

Conclusions: Palliative treatment with CMF should not be rejected for patients who have relapsed after adjuvant chemotherapy with the same modality.

Keywords: Breast cancer; Palliative CMF; Salvage chemotherapy; CMF retreatment

1. Introduction

Chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) is used as standard adjuvant treatment in premenopausal women with axillary-node-positive primary breast cancer. Patients who subsequently develop metastasis might be candidates for palliative chemotherapy. It is questionable whether reinstitution of CMF in this group of patients is a good choice.

In the literature several authors have studied the efficacy of systemic chemotherapy after the

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use of adjuvant chemotherapy in patients with advanced breast cancer [1–5]. The studies are often hampered by small numbers of patients and by the fact that palliative and adjuvant therapy were not the same.

In this article the results of palliative chemotherapy with CMF in 47 patients with advanced breast cancer, previously treated with the same regimen as an adjuvant to surgery, are reported.

2. Patients and methods

Fifty-six patients previously treated with adjuvant CMF received palliative CMF for advanced disease. The results of this therapy have been analyzed retrospectively.

The patients were treated in the University Hospital of Nijmegen and in the St. Anna Hospital, Oss, between 1976 and 1992.

Adjuvant CMF was given as "low dose" and "classical" before and after 1984 respectively and consisted of cyclophosphamide, days 1–14 orally, 75 and 100 mg/m^2 and on days 1 and 8 intravenous methotrexate, 30 and 40 mg/m^2 and 5-fluorouracil 500 and 600 mg/m^2 i.v. respectively. Cycles were repeated every 28 days. The number of cycles was 12 or more for the low dose and 6 for the classical CMF modality. Thus the intended total dose of CMF in the low-dose group during the first 6 cycles was about 77% of that of the classical one. But after 1 year this figure was 144%.

Palliative CMF as first-line chemotherapy was given as the classical modality. Indications were progressive metastatic or local/regional recurrent disease, steroid hormone receptor negativity or not (longer) sensitive to endocrine therapy. Patients with massive liver involvement or central nervous (CNS) metastasis received anthracyclins and CNS irradiation respectively. Patients should have received at least two cycles to be evaluable for response, unless there was clear progression after one cycle.

Response to therapy was established according to criteria of the WHO [6]. Age and menopausal status were considered at the start of palliative CMF treatment. Postmenopausal was defined as >1 year after the last menstruation or according to postmenopausal gonadotrophin levels in serum. Oestradiol receptor activity (ER) was determined in tissue of the primary tumour or metastasis with the dextran-coated charcoal ligand binding assay and Scatchard plot analysis with a cut-off value of 10 fmol/mg protein [7].

The estimated duration of response and survival was calculated according to Kaplan and Meier [13]. Tests for statistical significance were performed using SAS (Statistical Analyzing System) statistical software [8].

3. Results

University Hospital, Nijmegen

Between 1976 and 1992, adjuvant therapy with CMF was given to 226 women. Until 1994, local/regional or distant relapses have been observed in 111 patients. Of those women, 48 were treated with palliative CMF. The main reasons for withholding this therapy in the remaining patients were: no indication; refusal or relapse during adjuvant CMF therapy. Of the 48 treated patients, 8 were not evaluable for response to therapy because of: lack of tumour parameters ($n=2$); less than 2 cycles of therapy ($n=3$, for subjective toxicity); early death ($n=2$, fatal pulmonary embolism and unknown cause); and insufficient therapy ($n=1$). Thus, from this hospital 40 patients could be included in the analysis. [1]

St. Anna Hospital, Oss

The protocols for treatment of patients with breast cancer were identical to those in the University Hospital. From this hospital 8 patients eligible for analysis could be traced. One patient died within 2 months due to pneumonia. Seven were evaluable for response.

[1] One of these patients died after 1 month of therapy because of rapidly progressive disease. This was regarded as (early) failure to treatment.

Table 1
Pre-treatment characteristics and response to therapy

	Objective remission + stable disease / treated patients	%
Menopausal status		
Premenopausal	5/9	56
Postmenopausal	16/33	48
Unknown	1/5	20 NS
ER status		
Positive	11/21	50
Negative	10/21	48
Unknown	1/5	20 NS
Dominant site of disease		
Soft tissue	2/5	40
Bone	9/13	69
Viscera	11/29	38 NS
Prior endocrine therapy		
Yes	15/28	54
No	7/19	37 NS
Disease-free interval (DFI)		
< 12 months	1/4	25
> 12 months	21/43	49
Adjuvant CMF dose		
Low dose	13/23	56
Classical dose	9/24	38 NS

Results of palliative CMF (n = 47)

The interval between the two CMF regimens varied between 1 and 83 months. Prior palliative endocrine therapy was given to 28 patients (tamoxifen, $n = 25$ and/or oophorectomy).

Two of the 47 patients achieved a complete remission and 12 patients had a partial remission during treatment with CMF. The objective remission rate (CR plus PR) was 30% (14/47), with a median duration of response of 9.5 (range 5–21) months. In 8 patients the previously progressive disease stabilized with a median duration of 6 (range 3–17) months. The median survival time of patients who achieved an objective remission and stable disease was 20 (range 6–40) months, while the 25 patients who continued to have progressive disease had a median survival of only 6 (range 1–35) months ($p < 0.0001$).

The median survival time for the entire group was 12 (range 1–40) months.

A complete remission was found in 2 patients with visceral disease. The objective remission rates for patients with soft tissue, bone or visceral

Table 2
Response to palliative chemotherapy in relation to previous adjuvant chemotherapy

Ref. No.	No. of patients	Adjuvant therapy	Palliative therapy	Objective remission	
				n	%
(A) Palliative therapy same as adjuvant therapy					
1	29	CMF	CMF	12	41
This study	47	CMF	CMF	13	27
3	20	A/FAC	A/FAC	8	40
4	44	CFP	CFP	11	25
Total	140			45	32
(B) Palliative therapy different from adjuvant therapy					
3	18	A	various	7	39
4	156	CFP	various	43	28
6	15	various	various	4	27
7	25	CMF	Mi	7	28
Total	214			61	28
(C) No adjuvant therapy					
1	93	–	CMF	49	53
10	53	–	CMF	28	53
11	73	–	CMF	33	45
12	114	–	CMF	55	48
Total	333			165	50

C = cyclophosphamide; A = adriamycin; M = methotrexate; P = prednisone; F = 5-fluorouracil; Mi = mitoxantrone.

disease were 20, 41 and 28%, respectively ($p > 0.1$).

Four patients started palliative CMF chemotherapy within 12 months after finishing adjuvant CMF treatment. One of those patients achieved a partial remission; the other 3 patients continued with progressive disease.

Table 1 shows the relation between response to therapy (objective remission and stable disease) and pre-treatment characteristics. There was no statistically significant difference in response rates between patients with ER-positive and ER-negative primary tumours (7 of 21 and 6 of 21 respectively, $p > 0.1$) and between patients receiving one or more prior endocrine treatment modalities and patients without prior endocrine therapy (15 of 28 and 7 of 19 respectively, $p > 0.1$). Also no statistical significant difference in response rates between pre- and postmenopausal women was found (5 of 9 and 16 of 33 respectively, $p > 0.1$).

Finally, 7 of 23 and 7 of 24 patients who received low-dose and classical adjuvant CMF respectively achieved an objective remission. The objective remission plus stable disease percentages in both groups were 57 and 38, respectively (Table 1, $p > 0.1$).

4. Discussion

In this study the objective remission rate to palliative CMF chemotherapy in 47 women with advanced breast cancer who relapsed after adjuvant CMF was 30%.

Valagussa et al. [1] described the results of CMF retreatment in 29 patients; 41% of these achieved an objective remission, which in their series was not statistically significantly different from the results of CMF in 45 chemotherapy-naive patients (objective remission rate = 38%). In two other reports results of non-CMF palliative chemotherapy for patients pretreated with the same modalities resulted in objective remission rates of 25 and 40% [3,4].

The mean percentage of objective remissions for all patients treated with comparable regimens to their adjuvant therapy is 32% ($n = 140$, Table 2A). This is of the same order as the objective remission rates in patients treated with other regimens than those given in the adjuvant setting (mean objective remission rate = 28%, range 27–39%) [3–7] (Table 2B).

Remission rates for CMF in chemotherapy naive patients are reported as 45–53% in literature data between 1976 and 1991, covering our observation time [9–12].

The median duration of objective remissions in our study was 9.5 (range 5–21) months and compares well with that given for palliative CMF chemotherapy in general [9–12].

There were no statistically significant differences in remission rates in different catagories of patients according to the predominant localisation of disease, ER-status and menopausal status. However, the subgroups of patients were small.

One of 4 patients who relapsed within 12 months after the completion of adjuvant chemotherapy achieved an objective remission during palliative CMF treatment. In accordance, Buckner et al. [3] found no difference in response rates of patients who started palliative chemotherapy within 12 months or > 12 months after the completion of adjuvant treatment. In contrast, in Valagussa's study [1] no remission was seen in 6 patients who relapsed within 12 months after adjuvant chemotherapy.

It is of interest that "dose intensity" of adjuvant CMF did not influence the outcome of palliative chemotherapy. However, it should be recognized that the total amount of chemotherapy given was on average higher in the low-dose adjuvant CMF group than in the classical adjuvant CMF group.

As might be expected, survival times for patients who responded were better than for those who failed and this study reinforces the bad prognosis for the latter group (median survival of 6 months).

In conclusion, previous adjuvant CMF therapy does not exclude an objective response during palliative therapy with the same regimen in patients with advanced breast cancer. Although the objective remission rate in our study is inferior to that for chemotherapy-naive patients, palliative CMF therapy with its moderate and well-known

toxicity should not be rejected for patients who have relapsed after adjuvant CMF treatment.

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