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Commentary

Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: Are all CMFs alike?*

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Summary

The first reported effective adjuvant combination regimen for patients with operable breast cancer comprised oral cyclophosphamide (C) days 1–14 with intravenous methotrexate (M) and fluorouracil (F) on days 1 and 8, repeated every 28 days ('classical' CMF). These drugs have since been extensively used with or without endocrine therapies and/or other cytotoxics, as well as with radiation therapy to the chest wall yielding conflicting results. Although doses and schedules have varied widely, the combination of these three drugs has been generically referred to as CMF. Evidence exists that reducing the dose and/or altering the schedule of CMF ('modified' CMF) have compromised its efficacy in metastatic breast cancer. Reduction below standard dose of a similar regimen also gave inferior results in the adjuvant setting. In fact, the recently reported improved outcome of adding radiation therapy to CMF was only demonstrated in comparisons with a 'modified' CMF. Furthermore, trials in women with estrogen receptor-positive breast cancer, which did not demonstrate any significant benefit for the addition of adjuvant CMF to tamoxifen compared with tamoxifen alone, also used 'modified' CMF. Therefore, adherence to the 'classical' dose and schedule is recommended when CMF is used in adjuvant therapy.

Key words: adjuvant chemotherapy, breast cancer, CMF, radiotherapy, tamoxifen

Recently reported results from clinical trials investigating adjuvant treatments for breast cancer, raised the question about how much modification of an original treatment regimen can be made before therapeutic effectiveness is compromised. Specifically, to what extent are changes in dose, schedule, and timing or duration of regimens used in clinical trials responsible for an observed variability of treatment results. Two recent trials have shown that post-mastectomy irradiation added to a chemotherapy regimen containing cyclophosphamide, methotrexate, and fluorouracil ('CMF') improved disease-free and overall survival compared with 'CMF' alone [1, 2]. Furthermore, an editorialist wrote that "to the 30 percent reduction in breast-cancer deaths attributable to screening mammography and the proven benefit of adjuvant chemotherapy, we can now add further benefit from regional radiation treatment when combined with such chemotherapy" [3]. The CMF regimens used in these two radiation therapy trials were different from the CMF originally reported to improve disease-free survival and overall survival.

The 'classical' CMF combination comprised oral cyclophosphamide days 1–14 with intravenous methotrexate and fluorouracil on days 1 and 8, repeated every 28 days. It was originally designed to mimic the successful MOPP regimen used in the treatment of Hodgkin's disease, and became the first effective adjuvant chemotherapy regimen for breast cancer [4, 5]. Regimens containing the three ingredients – cyclophosphamide, methotrexate, and fluorouracil – have become collectively known as CMF despite considerable differences in schedule, dosage and route of administration compared with the 'classical' regimen. Such 'modified' CMF variants have been widely used.

Apparently conflicting results emerge from trials which investigate CMF together with tamoxifen as compared to tamoxifen alone in postmenopausal patients with estrogen receptor-positive breast cancer. While there is now, consistent evidence that anthracycline-based chemotherapy adds to the efficacy of tamoxifen for postmenopausal patients [6–8], the addition of CMF-type regimens to the antiestrogen compared with the endocrine agent alone does not always yield positive results.

The critical assumption is that the contribution of 'CMF' in these radiotherapy and endocrine therapy

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trials is the same as if no alterations in the doses and schedules of the drugs had been made. We believe this to be mistaken.

Several clinical trials provide evidence concerning the relative efficacy of different variants of the CMF regimen.

Drug dose reduction

Tannock et al. randomized 133 patients with metastatic disease to CMF (intravenous cyclophosphamide, methotrexate and fluorouracil at the doses of 600 mg/m^2, 40 mg/m^2, 600 mg/m^2, respectively) given on day 1 every three weeks ($C_{i.v.}$ MF D1) or to the same regimen using half of the dose of each drug. They demonstrated a reduction in response rate and overall survival with the lower dose CMF [9].

On the other hand, there is evidence that CMF retains some efficacy despite dose reduction. An EORTC trial in patients with operable breast cancer compared 24 months of low-dose CMF (cyclophosphamide 50 mg/m^2 orally on days 1 to 14, methotrexate 15 mg/m^2 intravenously on days 1 and 8, and fluorouracil 350 mg/m^2 intravenously on days 1 and 8) repeated every four weeks, to no-adjuvant treatment for women with node-positive disease. At 10 years median follow-up, there was a significant improvement in disease-free survival and overall survival for the 224 patients assigned CMF, compared to the 213 patients in the untreated control group [10]. A small trial in 90 patients with node-negative breast cancer with estrogen receptor-negative primaries who were randomized to receive $C_{i.v.}$ MF D1 or no adjuvant therapy also showed a treatment effect in terms of DFS favoring the CMF-treated patients [11].

Route of cyclophosphamide administration

Based on the assumption that compliance with oral cyclophosphamide would be less than with the same drug given through an i.v. injection, possibly due to increased nausea during the daily exposure, several studies and many care providers shifted to the latter regimen. This was done, however, without any direct evidence about the efficacy of $C_{i.v.}$ MF. In fact, no randomized trial has directly compared CMF regimens in which all three drugs were given intravenously on days 1 and 8 with those using 14 days of oral C and intravenous MF on days 1 and 8, either in the adjuvant or in the advanced disease setting. The studies described below involve other confounding factors such as total dose and dose intensity.

Multiple variations in schedule, dose intensity, and route of administration

Several trials have compared complex variations in CMF regimens in patients with advanced or recurrent disease. One trial involving 100 patients compared $C_{i.v.}$ MF D1 every three weeks *versus* a more intensive regimen in which cyclophospahmide (100 mg/m^2) was given orally, daily for 14 days every four weeks, together with weekly injections of methotrexate (20 mg/m^2) and fluorouracil (500 mg/m^2). After 20 weeks M and F were administered only on days 1 and 8 every four weeks [12]. The more intensive regimen was found to be significantly more effective in terms of response, and there was a trend to superior overall survival. Another trial, in 60 patients, compared $C_{i.v.}$ MF D1 every three weeks to 'classical' CMF every four weeks and failed to show a significant difference between the two regimens [13]. However, a larger trial conducted by the EORTC with 254 eligible patients, comparing the two regimens [14] concluded that the 'classical' CMF was superior in terms of response rate and overall survival. The authors attributed the superiority to the higher dose-intensity. These observations suggest that the antitumor efficacy of the 'classical' CMF regimen in metastatic breast cancer, just as in the adjuvant setting, depends on the dose and schedule of drug administration.

A Milan adjuvant therapy trial for patients with four or more involved axillary nodes compared a regimen of four courses of doxorubicin (75 mg/m^2) followed by eight courses of $C_{i.v.}$ MF D1 every three weeks *versus* an alternating regimen starting with two courses of $C_{i.v.}$ MF D1 followed by one course of doxorubicin, repeated for a total of 12 courses. All drug courses were recycled every three weeks. Treatment outcome was significantly superior for patients who received the sequential regimen (starting with full-dose anthracycline) compared with those given the alternating chemotherapy (starting with the 'less-than-optimal' $C_{i.v.}$ MF D1 regimen). The five-year relapse-free survival was 42% vs. 28% (P = 0.002) and overall survival was 58% vs. 44% (P = 0.002), respectively [15].

CMF added to tamoxifen

Does the available evidence support the combination of CMF plus tamoxifen as adjuvant therapy for postmenopausal women with operable breast cancer? A MEDLINE search identified six randomized trials with more than 120 patients, which directly compared CMF combined with tamoxifen to tamoxifen alone in postmenopausal patients [16–21] (Table 1). Also included in Table 1 is the recently published NSABP Trial B-20 which included both pre- and postmenopausal women with node-negative disease and endocrine-therapy responsive tumors [22]. The results of these trials appear to be in conflict with each other. Considering the three most recent trials, the Canadian trial in patients with node-positive, receptor-positive tumors showed that the addition of CMF to tamoxifen added toxicity but no benefit [21]. On the other hand, the International Breast Cancer Study Group (IBCSG) Trial VII demonstrated that the addition of three courses of 'classical' CMF to

Table 1. Trials of 'CMF'-type chemotherapy in combination with tamoxifen compared with tamoxifen alone.[a] In all trials CMF and tamoxifen were given concurrently.

Trial (ref.)	Population	Type of 'CMF' (doses in mg/sqm)	Number of patients[b]	Median follow-up (years)	Comments
IBCSG Trial III (Ludwig)[9]	Postm., N^+	C_{oral} 100 orally days 1–14 M 40 i.v. days 1, 8 F 600 i.v. days 1, 8 p (low-dose prednisone) Repeated every 28 days × 12	307	15 years	15-year DFS: CMF + pTAM[c] 35% vs. pTAM 21% ($P = 0.003$) Known ER^+ (103 patients): 15-year DFS: 26% vs. 24% (n.s.)
GROCTA[10]	Postm., N^+, ER^+	$C_{i.v.}$ 500 i.v. day 1 M 40 i.v. day 1 F 600 i.v. day 1 Repeated every 21 days × 6 followed by Epi × 4[d]	267	5 years	No significant benefit of CMF plus TAM *versus* TAM alone ($P = 0.1$)
SWOG[11]	Postm., N^+, ER^+	C_{oral} 60 orally, continuously M 15 i.v. weekly F 400 i.v. weekly V 0.625 weekly × 10 P (prednisone weeks 1–10) Treatment continuously for 12 months	598	6.5 years	5-year DFS: CT + TAM 75% vs. TAM 77% (n.s.)
Danish Trial 82C[12]	Postm., high risk of relapse	$C_{i.v.}$ 600 i.v. day 1 M 40 i.v. day 1 F 600 i.v. day 1 Repeated every 28 days × 9	1344	5 years	5-year DFS: CMF + TAM[e] 54% vs. RT + TAM 54% vs. TAM 45% (n.s.)
IBCSG Trial VII[13]	Postm., N^+, ER^+ Postm., N^+, ER^-	C_{oral} 100 orally days 1–14 M 40 i.v. days 1, 8 F 600 i.v. days 1, 8 Repeated every 28 days × 3	933 279	5 years	5-year DFS: Early CMF + TAM 64% vs. TAM 55% ($P = 0.02$) For ER^+: Early CMF + TAM 69% vs. TAM 57% ($P = 0.01$)
NCIC[14]	Postm., N^+, ER^+	$C_{i.v.}$ 600 i.v. day 1 M 40 i.v. day 1 F 600 i.v. day 1 Repeated every 21 days × 8	705	~ 5 years	5-year DFS: CMF + TAM 64% vs. TAM 61% (n.s.)
NSABP B-20[15]	Prem. and Postm., N^- with endocrine therapy-responsive tumors	C_{oral} 100 orally days 1–14 M 40 i.v. days 1, 8 F 600 i.v. days 1, 8 Repeated every 28 days × 6 or MF (M 100 i.v. followed by F 600 i.v. days 1, 8 and followed by leucovorin, repeated every 28 days × 6)	2307	~ 5 years	5-year DFS: CMF + TAM 90% vs. MF + TAM 89% vs. TAM 84% ($P < 0.01$)

[a] Six of these trials were identified in a MEDLINE search. We added NSABP Trial B-20 following its presentation at ASCO 1997.
[b] Number of patients relevant to the comparison of CMF + TAM *versus* TAM.
[c] pTAM: low-dose prednisone and TAM for one year.
[d] Epi: epirubicin following CMF.
[e] In this trial tamoxifen was given for 12 months.

tamoxifen improved five-year disease-free survival [20]. Furthermore, results from the NSABP Trial B-20 indicated that the addition of either 'classical' CMF or MF to tamoxifen yielded superior five-year disease-free survival [22].

We believe that variations in the schedule and dose explain the different efficacy of the CMF regimens used in these trials of adjuvant chemoendocrine therapy. A beneficial effect of adding CMF to TAM was exclusively seen in the three trials which used 'classical' CMF [16, 20, 22]. The trials in which CMF was given on day 1 every three or four weeks, or at a low continuous dosage (as in the CMFVP regimen) showed no such additional benefit [17–19, 21].

The interpretation of these trials requires consideration that the use of sub-optimal tamoxifen therapy as the control might give a false impression of the benefit of additional CMF. In IBCSG (Ludwig) Trial III [16], and in the Danish Trial 82c [19], endocrine therapy-alone control was administered for only one year. However, both IBCSG Trial VII [20] and NSABP Trial B-20 [22] showed benefit of the addition of 'classical' CMF when adjuvant tamoxifen was given for five years.

The large adjuvant trial, NSABP B-20, compared 'classical' CMF together with tamoxifen to tamoxifen alone. The trial included pre- and postmenopausal women with node-negative, endocrine-therapy-responsive breast cancer. There was also a treatment group which received the MF regimen with methotrexate, fluorouracil and leucovorin, but without cyclophosphamide [22]. At the time of the planning and activation of this trial, the results of the NSABP Trial B-19 (comparing CMF with MF), showing a significant disease-free survival benefit in favor of CMF [23] were still unknown. However,

unlike Trial B-19, both the 'classical' CMF and the MF regimens were equally effective, and yielded a significantly longer disease-free survival than tamoxifen alone. Cyclophosphamide might be a less important component of the combination in this setting, due to a potential negative interaction with tamoxifen. One interpretation of this set of apparently contradictory data might be that the schedule of drug administration is crucial to the efficacy of the CMF and MF regimens, when these are given together with tamoxifen.

'Modified' CMF added to radiation therapy, and 'modified' CMF as control treatment

The two recently published trials [1, 2] that claim the superiority of a combined CMF and radiation therapy regimen over a CMF-only control group used a 'modified' CMF regimen in both treatment arms. The CMF regimens used were intravenous cyclophosphamide, methotrexate and fluorouracil at the doses of 600 mg/m^2, 40 mg/m^2, 600 mg/m^2, respectively) given on day 1 every three weeks ($C_{i.v.}$ MF D1 q 21 days) for the Canadian trial [2] and every four weeks for the Danish trial ($C_{i.v.}$ MF D1 q 28 days) [1]. There might well be an additive effect of CMF and radiation therapy, which explains the success of the combined treatment. There is no doubt, however, that the 'reduced' CMF cannot be considered as a reasonable control for testing this success. The correct, though limited, conclusion from these two trials should be: 'Radiation therapy to the chest wall and regional nodes should be considered for premenopausal patients with high-risk of relapse in all cases in which suboptimal systemic therapy is planned' [24].

Conclusions and implications

The 'classical' CMF regimen was originally formulated based upon the highly effective MOPP regimen, comprising two weeks of cytotoxic treatment and two weeks of treatment-free interval for recovery. Long-term results [5] and other information available to date show that this 'classical' CMF regimen is safe, does not cause long-term toxicity, and offers additional efficacy when given in combination with tamoxifen in any risk group. It seems important that the adjuvant CMF regimen be given as closely as possible to the way it was first used by Bonadonna [4]. More than a quarter of a century of attempts to alter the regimen by reducing the doses of its components or by modifying its schedule do not seem to have yielded any improvement over the classical regimen. Future clinical research is unlikely to contribute new information on this subject. It is recommended [25] that attempts to further improve cytotoxic treatments should be based on improved understanding of the biology of relapse, or the use of novel combinations, rather than by including inferior or untested variations of the CMF regimen in clinical trials.

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