CMF revisited in the 21st century

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Over the last 35 years, classical CMF (combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil) has been a milestone in the adjuvant treatment of women with breast cancer. However, after an early burst of success lasted just over 10 years, classical CMF has been supplanted by ‘third-generation’ regimens containing taxanes and anthracyclines. Questions have been raised in the past years concerning the true effectiveness of adjuvant CMF for specific subgroups of patients and particularly, recent retrospective data support the fact that the CMF might have a role in the treatment of patients with triple-negative breast cancer. One possible justification for supporting this role of CMF may be sought in the mechanism of action of drugs used in the regimen, as triple-negative cells may be sensitive to alkylating agents that cause double-strand breaks in DNA. The lesson learned from the CMF could lead us to identify new combinations of drugs that could include the optimal chemotherapy backbone for triple-negative breast cancer such as platinum compounds or alkylating agents or Poly (ADP-ribose) polymerase inhibitors.

In conclusion, although we have learned a lot from the use of CMF, many questions are still open and hopefully stimulate our thinking, as clinicians, leading us to find new and more effective ways to treat breast cancer.

Key words: adjuvant chemotherapy, alkylating agents, breast cancer, classical CMF, triple-negative, tumor heterogeneity

"Don’t bury me ‘cause I’m not dead yet.”
Elvis Costello

introduction

A pioneer in the field of medical oncology, classical CMF (combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil) is facing hard times as most medical oncologists prefer the so-called ‘third-generation regimens’ with anthracyclines and taxanes as adjuvant treatment for women with operated breast cancer. Because our field of medical oncology is only a few decades old, CMF has been one of our leaders for much of our history, leaving an indelible mark on our specialty.

Since 3 July 1973, when the first patient was enrolled in the first adjuvant Milan trial [1], CMF has certainly been a milestone in the adjuvant treatment of women with breast cancer.

The success of CMF remained unchallenged until the mid-80s when anthracyclines appeared on the scene. Subsequently, the stature of CMF was further threatened in the nineties when the taxanes made a dramatic entrance on the scene of chemotherapy worldwide.

In this brief review, we would like to pay a tribute to CMF, highlighting the great contribution that it made to oncology and particularly to the treatment of women with breast cancer.

As clinically oriented medical oncologists, we would like to investigate whether, after observing the classical CMF being overtaken by more modern regimens, it should continue to have a place in the care of at least a subgroup of patients.

portrait of CMF: deeds and misdeeds

We can set the birth of the classical CMF in Milan (Italy) in the early seventies, although few years before Paul P. Carbone reported initial National Cancer Institute data on a quadruple drug regimen containing cyclophosphamide, methotrexate, fluorouracil and prednisone for advanced breast cancer patients [2]. CMF was originally designed to resemble the MOPP (combination chemotherapy with mechloretamine, vincristine, procarbazine and prednisone) scheme used successfully in the treatment of Hodgkin’s disease, which includes 2 weeks of cytotoxic treatment and 2 weeks interval without treatment for recovery [3]. In 1976, CMF efficacy as adjuvant treatment for node-positive breast cancer patients was firstly reported by Bonadonna et al. [1]. These results, along with those reported in a similar population of patients by the National Surgical Adjuvant Breast and Bowel Project (NSABP), raised hopes that chemotherapy could have a more central role in the primary management of breast cancer [4].
The original CMF regimen consisted of cyclophosphamide (100 mg/m² orally from day 1 to 14), methotrexate (40 mg/m² i.v. on days 1 and 8), and fluorouracil (600 mg/m² i.v. on days 1 and 8), repeated every 4 weeks.

In 1989, during the Karnofsky lecture at the American Society of Clinical Oncology, Bonadonna [5], based on the studies of the Istituto Nazionale Tumori started in 1973, 1975 and 1985, concluded that in premenopausal women with primary node-positive disease, classical CMF for six cycles could be considered a standard.

The role of tamoxifen in premenopausal women was not yet understood and part of the benefit in younger women was also attributed to the effect on the endocrine ovarian suppression exerted by the CMF.

In postmenopausal women with estrogen receptor (ER)-positive tumors, tamoxifen was recommended, while women with ER-negative tumors had an advantage from the classical CMF.

In women with node-negative and ER-positive tumors, tamoxifen was recommended, while in the ER-negative tumors, classical CMF for six cycles offered a significant advantage both on relapse-free survival (RFS) and overall survival (OS) [6, 7].

**CMF-like regimens and the classical CMF**

During the following years, all regimens containing the three ingredients—cyclophosphamide, methotrexate and fluorouracil—have become collectively known as CMF, despite significant differences in schedule, dosage and route of administration compared with the ‘classical regimen’ initially tested in Bonadonna’s studies. These modified schedules have been widely used without the support of a direct comparison between the classical CMF regimen and the variants [8].

Indeed, over the years, many oncologists have changed the classical CMF schedule by switching cyclophosphamide administration from oral to i.v., based on the empirical assumption that compliance would have been better. However, no randomized trial has directly compared CMF regimens in which all three drugs were given i.v. on days 1 and 8 with those using 14 days of oral cyclophosphamide and MF i.v. on days 1 and 8, either in the adjuvant or advanced disease (Table 1).

Only two studies compared classical CMF with i.v. CMF (schedule 1, 21) in metastatic breast cancer patients [12, 13]. The results of the European Organisation for Research and Treatment of Cancer trial showed a better response rate and time to progression for the classical CMF, and further emphasized the importance of cyclophosphamide dose intensity delivered orally as compared with i.v. [13].

However, there is currently no evidence that oral cyclophosphamide is either more toxic or more or less effective than an equivalent dose of i.v. cyclophosphamide [14].

Moreover, during the first 10 years, adjuvant classical CMF survived many other schemes including combination with other drugs, as leukenar, nitrogen mustard, and vincristine,

### Table 1. CMF-like and cCMF trials: doses, duration, and schedule

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Setting</th>
<th>Trial design</th>
<th>Doses and schedule (mg/m²)</th>
<th>Duration</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSES</td>
<td>EORTC 452</td>
<td>Adj</td>
<td>LD CMF versus no treatment i.v. CMF versus half-dose CMF</td>
<td>C 50 os, days 1–14, 28; M 15 i.v., days 1, 8–28; F 350 i.v., days 1, 8–28</td>
<td>24 months</td>
<td>CMF better</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Toronto, Canada 133</td>
<td>Met</td>
<td></td>
<td>C 600/300 i.v., 1–21; M 40/20 i.v., 1–21; F 600/300 i.v., 1–21</td>
<td>NA</td>
<td>i.v. CMF better</td>
<td>[6]</td>
</tr>
<tr>
<td></td>
<td>INT, Milan 90</td>
<td>Adj (N+, ER−)</td>
<td>i.v. CMF versus no treatment i.v. CMF versus no treatment</td>
<td>C 600 i.v., 1–21; M 40 i.v., 1–21; F 600 i.v., 1–21</td>
<td>12 cycles</td>
<td>CMF better</td>
<td>[7]</td>
</tr>
<tr>
<td>SCHEDULE</td>
<td>Italian trial 68</td>
<td>Met</td>
<td>i.v. CMF versus cCMF</td>
<td>C 600 i.v., 1–21 or 100 os, 1–14, 28; M 40 i.v., 1–21 or 1, 8–28; F 600 i.v., 1–21 or 1, 8–28</td>
<td>NA</td>
<td>No difference</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>EORTC Trial 10808 254</td>
<td>Met</td>
<td>i.v. CMF versus cCMF</td>
<td>C 600 i.v., 1–21 or 100 os, 1–14, 28; M 40 i.v., 1–21 or 1, 8–28</td>
<td>NA</td>
<td>cCMF better</td>
<td>[9]</td>
</tr>
<tr>
<td>DURATION</td>
<td>Tancini 466</td>
<td>Adj</td>
<td>cCMF ×6 versus ×12</td>
<td>C 100 os, days 1–14, 28; M 40 i.v., days 1, 8–28; F 600 i.v., days 1, 8–28</td>
<td>6 or 12 cycles</td>
<td>No difference</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td>Ludwig 1275</td>
<td>Adj</td>
<td>PeriopCMF versus cCMF</td>
<td>C 400 i.v., days 1–8; M 40 i.v.; F 600 i.v.; L 15 i.v.</td>
<td>1 or 6 cycles</td>
<td>cCMF ×6 better</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>IBCSG-VI; GBCSG 735; 289</td>
<td>Adj</td>
<td>cCMF ×3 versus ×6</td>
<td>C 100 os, days 1–14, 28; M 40 i.v., days 1, 8–28; F 600 i.v., days 1, 8–28</td>
<td>3 or 6 cycles</td>
<td>cCMF ×6 better</td>
<td>[12]</td>
</tr>
</tbody>
</table>

C, cyclophosphamide; M, methotrexate; F, fluorouracil; c, classical; EORTC, European Organisation for Research and Treatment of Cancer; LD, low dose; INT, Istituto Nazionale Tumori; ER, estrogen receptor; Adj, adjuvant; Met, metastatic; os, oral; NA, not assessed; N, node; Periop, perioperative; L, leucovorin; GBCSG, German Breast Cancer Study Group; IBCSG, International Breast Cancer Study Group.
showing its superiority in terms of disease-free survival (DFS) and OS [15–18].

In 2005, Bonadonna et al. [19] further emphasized that CMF after 30 years is still an effective regimen with long-lasting benefit maintained in patients with both favorable and unfavorable prognostic indicators, at the cost of minimal long-term sequelae.

the decline of CMF and the rise of anthracyclines and taxanes

Although after 30 years of follow-up CMF continues to show a significant benefit for RFS and OS compared with no chemotherapy [20], classical CMF was used as a comparator only in few clinical trials.

In the direct comparison, a total of eight trials of anthracyclines versus classical CMF have been identified and summarized in Table 2 [20, 24–30]. Three of them showed a better OS/DFS for the anthracycline-containing arm [20, 28, 30] and the remaining trials showed no difference.

In the Early Breast Cancer Trialists’ Collaborative Group overview, among 11 studies of anthracycline-based regimens compared with CMF (total N = 5942 patients), only one study found a lower recurrence rate for CMF treatment, but this trial compared only one cycle of an anthracycline-containing regimen with six cycles of low-dose i.v. CMF [31]. The meta-analysis showed that compared with CMF (any schedule), anthracycline-based regimens produced a 12% proportional reduction in recurrence (P = 0.006; absolute benefit 3.2%) and an 11% proportional reduction in mortality (P = 0.02; absolute benefit 2.7%) [32]. However, the patient population in this meta-analysis included both pre- and postmenopausal women (~70% of the women in this analysis were aged <50 years) with both hormone receptor-positive and hormone receptor-negative disease.

Specifically in the subset of women aged <50 years, there was a 13% reduction in risk of recurrence (P = 0.01) and a nonsignificant (P = 0.09) reduction in mortality with anthracycline-based regimens compared with CMF [33].

In advanced breast cancer, the taxanes, docetaxel and paclitaxel, are among the most active chemotherapeutic agents currently in use. However, in the adjuvant setting, trials of taxanes have not been conclusive in showing an advantage over CMF mainly because no direct comparison has been done [34–37].

Two trials, Cancer and Leukaemia Group B (CALGB) 9344 and NSABP B-28, compared anthracycline–taxane experimental regimens with the standard doxorubicin and cyclophosphamide regimen (AC) and, thus, were indirectly comparable with classical CMF, based on the results of the NSABP B-15 trial [25].

CALGB 9344 trial [36] compared four cycles of 60–90 mg/m² doxorubicin and cyclophosphamide followed by 175 mg/m² paclitaxel infused over 3 h with four cycles of 60–90 mg/m² doxorubicin and cyclophosphamide alone.

The resulting proportional reduction in mortality was 13%. Results showed that 60 mg/m² doxorubicin followed by 175 mg/m² paclitaxel is favored clinically. Unfortunately, the study did not report on activity outcome for the three doxorubicin groups separately, which would have provided a more accurate measure of activity for the 60 mg/m² doxorubicin followed by 175 mg/m² paclitaxel regimen.

The second anthracycline–taxane trial, the NSABP B-28 [38], compared an almost identical anthracycline–taxane regimen (four cycles of AC60) with that in the CALGB 9344 and showed no significant survival benefit. Although longer treatment can improve outcome, the addition of four cycles of paclitaxel to four cycles of AC did not improve OS consistently compared with AC alone.

Of the 19 trials assessing the role of taxanes in the adjuvant treatment of breast cancer, there are four trials comparing the taxane-containing regimen with an anthracycline-based treatment known to be more active than classical CMF as summarized in Table 3 [39–42]. Interestingly, among these trials, only two have anthracycline-based regimens, which have previously shown superiority over classical CMF [28, 43], as a control arm. Nevertheless, the other two trials have a sequential anthracycline–CMF treatment as a control arm, which is very similar to the sequential epirubicin–CMF regimen proven to be more effective than CMF in the UK trial [43]. In these trials, RFS was significantly better for the taxane arm in three of them and data about OS are not yet conclusive.

However, there are some limitations in interpreting these results from recently reported taxane-based adjuvant trials that consist in the use of an anthracycline-based control arm that is

Table 2. Anthracycline-based trials compared with classical CMF

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Nodes</th>
<th>Anthracycline regimen (dose mg/m²)</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onco-France²</td>
<td>249</td>
<td>Positive</td>
<td>A30VCF ×12</td>
<td>AVCF better (OS/DFS)</td>
<td>[21]</td>
</tr>
<tr>
<td>Sweden</td>
<td>43</td>
<td>Positive</td>
<td>A40C ×6</td>
<td>No difference</td>
<td>[22]</td>
</tr>
<tr>
<td>NSABP B-15</td>
<td>2194</td>
<td>Positive</td>
<td>A60C ×4 ± CMF i.v.</td>
<td>No difference</td>
<td>[23]</td>
</tr>
<tr>
<td>GUN3-Italy</td>
<td>220</td>
<td>Positive</td>
<td>CMF/E75Vc ×6</td>
<td>No difference</td>
<td>[14]</td>
</tr>
<tr>
<td>Belgium</td>
<td>777</td>
<td>Positive</td>
<td>E60C 1–3/E100C ×8</td>
<td>No difference</td>
<td>[15]</td>
</tr>
<tr>
<td>NCI-C MA.5</td>
<td>710</td>
<td>Positive</td>
<td>CE60F 1–8 ×6</td>
<td>CEF better (OS/DFS)</td>
<td>[16]</td>
</tr>
<tr>
<td>SWOG8897</td>
<td>2691</td>
<td>Negative</td>
<td>FA30C 1–8 ×6</td>
<td>FAC better (OS/DFS)</td>
<td>[17]</td>
</tr>
<tr>
<td>NSABP B-23</td>
<td>2008</td>
<td>Negative</td>
<td>A60C ×4</td>
<td>No difference</td>
<td>[18]</td>
</tr>
</tbody>
</table>

²Classical CMF ×12 cycles.
C, cyclophosphamide; M, methotrexate; F, fluorouracil; A, doxorubicin; V, vinca alkaloid; OS, overall survival; DFS, disease-free survival; NSABP, National Surgical Adjuvant Breast and Bowel Project; E, epirubicin; Vc, vincristine.
no more effective than classical CMF, the interference of the endocrine effects of chemotherapy in premenopausal patients with hormone receptor-positive tumors and, finally, the lack of subgroup analysis that differentiates node-positive from node-negative patients.

**breast cancer is heterogeneous: is there a role for classical CMF in triple-negative disease?**

Questions have been raised in the past years concerning the true effectiveness of adjuvant CMF for specific subgroups of patients. Early studies suggested that Human Epidermal growth factor Receptor 2 (HER-2/neu)-positive tumors do not benefit from CMF-based chemotherapy that, by contrast, has a considerable effect in tumors with no or minimal expression of this oncogene. The notion that breast cancer is a heterogeneous disease has been around for many years, but in the past years, few investigators have had the perseverance to analyze the effects of adjuvant chemotherapy in clinically relevant subgroups (e.g. ER-negative or low-ER, intermediate-ER and ER-rich disease). More recently, intrinsically different subtypes of breast cancer based on genetic profile and Immunohistochemistry (IHC) determination of selected targets have been identified [44, 45]. Perou et al. [44] demonstrated that the phenotypic diversity of breast tumors was associated with corresponding gene expression diversity. Using this subset, the authors were able to identify four different molecular subtypes of breast cancer: ER-positive/luminal-like, basal-like, HER-2/neu-positive, and normal breast. Subsequent data expanded the classification to distinguish between luminal A and luminal B [45].

The recognition of a specific target or a feature within a homogeneous subgroup of patients results in the identification of specific and biologically targeted adjuvant treatments. NSABP B-13 and B-19 [46] randomized clinical trials carried out to evaluate the use of adjuvant chemotherapy for the treatment of patients with node-negative ER-negative tumors showed that both MF and CMF are effective therapies for patients with ER-negative tumors and negative axillary nodes. In patients aged ≤49 years, CMF results in a clearly better DFS and survival than does MF, whereas in patients ≥50 years of age, a benefit from both regimens is apparent, although it is less clear which regimen is more effective.

Long-term findings of the NSABP B-20 trial [47] show that the benefit from adding CMF to tamoxifen is inversely related to the quantitative concentration of tumor ERs. A previous study by Rakha et al. [48] has suggested that the negative prognosis of the triple-negative phenotype may be alleviated by adjuvant chemotherapy. In that study, patients with triple-negative breast cancer who received adjuvant chemotherapy following primary surgery were uniformly treated with CMF. This raises the intriguing possibility that regimens including antimetabolites and high cumulative doses of alkylating agents such as cyclophosphamide may be more effective than anthracycline-based chemotherapeutic regimens in triple-negative tumors. A recent study in the preoperative setting further supports this hypothesis by clearly identifying p53-mutant ER-negative tumors as those most sensitive to high-dose alkylating agents and allowing very high levels of pathological Complete Response in triple-negative tumors treated with dose-intense cyclophosphamide [49]. In this context, CMF chemotherapy, being not inferior to anthracycline-containing therapy in patients with tumors lacking overexpression of topoisomerase II [50] or with HER-2/neu-negative breast cancer [51], may have a role as adjuvant therapy in patients with triple-negative tumors, particularly those patients with relatively small node-negative tumors.

Falo et al. [52] recently published a trial in a series of operable breast cancer patients treated with primary CMF chemotherapy. In this series, 300 patients with operable breast cancer were treated with primary CMF1-8 i.v. HER-2/neu overexpression or amplification was found in 23.66% cases. Univariate analysis showed that response was similar in HER-2/neu-positive and -negative tumors (51.38% versus 47.36%, $P = 0.6$). Triple-negative tumors presented the highest response rate (64.9%). Patients with the combination of response to CMF and HER-2/neu-negative tumors presented the best outcome. On the other hand, the association of no response to CMF and positive HER-2/neu score was statistically related to poor DFS and OS.

Furthermore, tissue blocks from patients of MA5 trial were recently analyzed for ER, progesterone receptor, HER2, Ki67, CK5/6 and epidermal growth factor receptor and for tissue microarray to determine the biological subtype [53]. The results showed that in the CEF (cyclophosphamide, epirubicin,
and fluorouracil) arm, patients with core basal tumors had a hazard ratio (HR) of 1.8 (log-rank $P = 0.02$) for OS relative to the other biological subtypes. In the CMF arm, there was no significant difference (HR 0.9, $P = 0.7$). The interaction between core basal status and treatment was borderline significant ($P = 0.06$). RFS differences did not reach significance. Authors concluded that data from this randomized trial support the hypothesis that anthracycline-containing adjuvant chemotherapy regimens are inferior to adjuvant CMF in women with basal-like breast cancer.

These results further support previous reports in which early breast cancer patients with negative hormone receptors have less or even no survival advantage with anthracycline-based adjuvant chemotherapy compared with non-anthracycline regimens [51, 54].

Recently, a retrospective study by Colleoni et al. highlights a larger magnitude of benefit of classical CMF in patients with triple-negative node-negative breast cancer after a median follow-up of 11 years. In this report, authors explored patterns of recurrence according to treatment received in a group of patients ($n = 2257$) enrolled in International Breast Cancer Study Group trials VII–IX with node-negative breast cancer, randomly assigned to receive classical CMF for three or six cycles with or without endocrine therapy versus endocrine therapy alone. Patients with triple-negative tumors were 303 (15%) and chemotherapy significantly improved 10-year DFS in this subtype group (73% versus 57%, $P = 0.007$) [55].

conclusions
what we have learned from CMF?
After an early burst of success lasted just over 10 years, classical CMF has been supplanted by more toxic and more expensive regimens, so-called third-generation regimens, containing taxanes and anthracyclines.

However, while the CMF regimen is old and is a very ‘first-generation’ regimen, it certainly has at least three points in its favor. First, CMF has a safe and very well-known toxicity profile based on data now older than 35 years and well consolidated. Secondly, recent retrospective data support the fact that the CMF might have a role in the treatment of patients with triple-negative breast cancer. The last point—not to be underestimated—is certainly an economic point, CMF being a not-expensive scheme.

Willing to look forward, we should ask how to take advantage of the positive points that we learned from the CMF, and especially how to use these strengths to improve our skills to treat breast cancer patients.

One of the main limitations that we stressed throughout this review derives from the interference due to populations with hormone receptor-positive disease included in studies, which may benefit from chemotherapy. Furthermore, the data published so far, in most cases, were interpreted on heterogeneous populations including patients with either positive or negative axillary lymph nodes and with hormone receptors or HER-2/neu positive or negative. But when analyzed by subgroups, the proper niche of patients for each treatment may be identified. This point may serve as an opportunity for opening a discussion in favor of the use of classical CMF chemotherapy, which might still have role, for instance, as effective adjuvant systemic therapy for triple-negative node-negative population [55].

One possible justification for supporting this role of CMF may be sought in the mechanism of action of drugs used in the CMF regimen. In vitro chemosensitivity studies have found that human cells lacking BRCA1, and to some extent other triple-negative cells, may be sensitive to drugs that cause double-strand breaks in DNA, such as alkylating agents, [50] and less sensitive to doxorubicin, as well as to paclitaxel [56].

Moreover, methotrexate and 5-fluorouracil used in CMF regimens are both antimetabolites, which are more suitable for the higher proliferative index of triple-negative breast cancers [55].

To further support the notion of breast cancer heterogeneity, it has been recently reported that the category of triple-negative tumors can be additionally divided into subtypes [57]. In consequence, the response to various agents may differ depending on the intrinsic molecular subtypes. For example, as previously reported, the subgroup of p53-mutant ER-negative tumors has proved to be more sensitive to high-dose alkylating agents [49].

Another possible limitation is that over the years CMF has not been directly compared with a taxane-containing regimen, and this information is lacking especially within the triple-negative subgroup.

For this purpose, it would be interesting to explore the combination of taxanes with alkylating agents or platinum compounds, which are the backbone of regimens for triple-negative breast cancers, compared with classical CMF.

Finally, recent results from preclinical and clinical studies have highlighted poly (ADP-ribose) polymerase (PARP) inhibitors as one of the most promising ‘targeted therapies’ for metastatic triple-negative breast cancer, DNA repair being the intended ‘target’ [58, 59].

Looking at the future development of these agents, one challenging task might consist in further defining triple-negative patients most likely to respond to PARP inhibitors and determining the optimal chemotherapy backbone to combine with them.

This direction is particularly important as these drugs move to the adjuvant setting because long-term toxic effects to normal tissues as a result of prolonged suppression of DNA repair have yet to be defined.

In conclusion, although we have learned a lot from the use of CMF, many questions are still open and hopefully stimulate our thinking, as clinicians, leading us to find new and more effective ways to treat breast cancer.

disclosure
The authors declare no conflict of interest.

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