Chemotherapy Versus Combination of Chemotherapy and Endocrine Therapy in Advanced Breast Cancer

A Prospective Randomized Study

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One hundred-forty-five postmenopausal women with metastatic breast cancer entered a prospective randomized trial comparing treatment A (cyclophosphamide, methotrexate, and 5-fluorouracil; CMF) with treatment B (the same chemotherapy plus tamoxifen; CMF plus T). Patients on treatment A had T added to CMF at the time of progression or relapse (second-line CMF plus T). One hundred thirty-three cases were evaluable. Considering response rate to first-line treatment, CMF plus T appeared to be significantly superior to CMF alone (74% versus 51%), respectively; $P < 0.01$). Median time to failure to first-line treatments, considering all patients, was longer in CMF plus T than in CMF arm (48 and 24 weeks, respectively; $P = 0.06$). Considering patients showing objective remission, median duration of response to CMF was similar to that of CMF plus T (47 and 51 weeks, respectively). Twelve of 39 evaluable women treated with second-line CMF plus T showed objective responses (31%). Median time to failure to treatment procedures scheduled in arm A (CMF → CMF + T) was longer than that to treatment in arm B (CMF plus T) (56 and 48 weeks, respectively; $P = 0.08$). Median survival was longer in patients randomized to treatment A (111 weeks) than in patients randomized to treatment B (78 weeks), but this difference was not statistically significant ($P = 0.25$). It can be concluded from this study that a combination of endocrine therapy and chemotherapy is significantly more active than chemotherapy alone in inducing an objective remission. This strategy of treatment is advisable in situations urgently requiring a clinical response. However, as a sequence of chemical and endocrine therapy induced a longer time to development of progressive disease and a better survival, sequential therapy is advisable for common clinical use.


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systemic treatments which at some point include either chemical or endocrine regimens should be usefully applied.

Progress of clinical research in this field could possibly be investigated by comparing the results obtained by the concurrent application of combination chemotherapy and endocrine therapy with those obtained by separate use of each single modality. The authors think that the best comparison to be made is between chemohormonal therapy versus combination chemotherapy, which is known to have a higher response rate than endocrine therapy. Endocrine and cytotoxic chemotherapy have different mechanisms of action, they do not have overlapping toxicity, and breast carcinoma is considered as having heterogeneity with reference to estrogen receptor content at a cellular level and as containing, in any case, at least a minimum number of endocrine characterized cells. The few available studies on this subject seem to deny the theoretical reasoning that synchronization of cells in a rest phase by endocrine therapy would protect them from the cytotoxic agent, so that response rate could be adversely affected.

The current study compares, in a prospective randomized fashion, the effects produced by the classical chemotherapy regimen of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with those produced by the same regimen plus tamoxifen (T) in advanced breast cancer. The patients on CMF were required to add T at the time of progression or relapse. Our aims were the following: (1) to make a comparison of remission rate, time to failure and duration of remission between the two first-line treatments (chemotherapy alone versus concurrent chemotherapy and endocrine therapy); (2) to make a comparison of time to failure and of total survival between the two therapeutic procedures; i.e., the sequential or the concurrent use of endocrine therapy and combination chemotherapy.

Materials and Methods

Eligibility Criteria

One hundred forty-five consecutive patients with metastatic breast cancer, who were eligible for the study, were entered in this trial. Eligibility requirements were that patients be in postmenopause and had not received prior cytotoxic chemotherapy. Patients who had received prior endocrine therapy, apart from estrogens or antiestrogens, were eligible. Patients who entered this study after an endocrine treatment had to show progression or relapse. In the case of additive hormonal treatment, the drug had to be discontinued at least four weeks before entering the study, and patients could not have shown any improvement during two consecutive observations at least seven days apart after discontinuing the hormone.

All cases were required to show measurable and/or evaluable disease. They were not acceptable if the only manifestation of the disease was pleural effusion or mixed osteoblastic and osteolytic lesions, or if they had metastases of the central nervous system. At entrance into the protocol, WBC had to be >4000, platelet count >120,000, serum creatinine level, <1.5 mg/dl, bilirubin <1.5 mg/dl. Estrogen receptor assay was not mandatory for entering patients on this trial. However, it was performed in patients from the Parma Center whenever a soft tissue lesion was available for biopsy, on the condition that the disease continued to be measurable or evaluable. Estrogen receptor analyses were performed by the dextran-coated charcoal technique. Specimens containing <3 fmols of receptor/mg of cytosol protein were considered negative.

Treatment Groups

The design of the study is indicated in Figure 1. Responses to treatment are referred to as complete response (CR), partial response (PR), no change (NC), and progressive disease (P). Patients were randomized to one of two treatment groups. Group A: treatment with CMF (cyclophosphamide, 100 mg/m² orally, day 1–14; methotrexate, 40 mg/m² intravenously (IV); and 5-fluorouracil, 600 mg/m² IV, day 1 and 8, cycle repeated every four weeks). Group B: treatment with CMF as in Group A plus T, 10 mg twice daily. Patients were stratified by the institution and according to dominant site of the disease, free interval, time after menopause and whether they had received previous endocrine treatment. Patients 60 years of age and older and/or with diffuse osseous metastases received a lower dosage of methotrexate and 5-fluorouracil (30 mg/m² and 400 mg/m², respectively). At 8 courses after obtaining a complete response or 12 courses after obtaining a partial response, chemotherapy was administered at alternate courses. The two types of treatment were continued until either progression of disease or relapse occurred. They were compared by response rate, time to failure in all patients, response duration in responding patients and survival. The study protocol indicated that patients on CMF were required to receive T, in addition to CMF, at the time of progression or relapse. Patients failing to respond to treatment procedures scheduled both in Group A and in Group B of the study received, whenever possible, a regimen containing Adriamycin. Successive regimens were at the discretion of the physician and were individualized.
Objective Response

Objective response was assessed using the system recommended by the UICC. However, patients having mixed or blastic bone lesions before or after therapy were never considered as having a complete response. The first evaluation of objective response was performed after a minimum of eight weeks of treatment. In patients receiving second-line CMF plus T, a second evaluation of objective response was performed. On that occasion, patients showing no improvement and discontinuing treatment after a minimum of four weeks were considered as having progressive disease.

Time to Treatment Failure, Duration of Response and Survival

Time to treatment failure was calculated from the beginning of therapy until progression or relapse became objectively evident. Duration of response was calculated from the beginning of therapy until relapse. Response duration to second-line CMF plus T was calculated from the time of addition of T. Survival was dated from time of beginning of treatment to death. Median response duration and survival were analyzed by Kaplan and Meier's actuarial method. Comparisons of differences in response duration or survival were made using Cox's method.

Review Committee

Response to treatment in all patients was assessed by a Review Committee composed of three medical oncologists of the Parma Center Staff. Bone radiographs were re-examined by the above members together with a radiologist.

Results

A total of 145 patients entered the trial: 74 were randomized to receive CMF (Group A) and 71 to receive CMF plus T (Group B). Response to treatment could be evaluated in 133 patients; 71 on CMF and 62 on CMF plus T. Twelve patients who discontinued treatment or died before the time of the first evaluation, were considered non evaluable. The reasons for discontinuation of treatment were: psychological refusal (A:1, B:1), acute hepatitis arising during the first cycle (B:2); neither of the last two patients had progressive disease and both recovered. The causes of death were: cardiac failure or myocardial infarction (B:2), sudden death at home (A:1, B:1), toxic granulocytic infection possibly contributing to death (B:2), disease progressing too rapidly for assessment (A:1, B:1).

Median age of patients in Group A was 57 years (range, 37–79 years) and 58 years in Group B (range 33–75 years). Most patients were ambulatory and suitable for outpatient therapy.

Both treatment groups were statistically comparable with respect to characteristics which might affect the likelihood of response to chemotherapy or endocrine therapy (Table 1). Fifty-six of 133 patients (42%) had been previously submitted to endocrine treatment. An identical number of patients were administered reduced dosage of methotrexate and 5-fluorouracil by age ≥60 (27 on A and 28 on B) or by diffuse osseous metastases (7 on A and 6 on B).

Table 2 summarizes the types of response to the two first-line regimens. The overall response rate for the chemical-endocrine regimen (Group B) appears to be...
in patients with 0–1, 1–5, >5 years) while response rate to chemotherapy alone was unchanged. The differences between the two types of treatments were practically identical regardless of whether the patient had previous endocrine treatment. Indeed, the response rate tended to be significantly higher in the chemical endocrine group (CMF plus T) than in the chemotherapy group (CMF) even in patients previously untreated with any type of systemic therapy (51 versus 75%; \( P < 0.06 \)).

Objective remissions according to site of metastases are shown in Table 4. The number of single visceral lesions was too small for any comparative consideration. Difference in favor of the chemical endocrine treatment was rather relevant in breast lesions (73 versus 47%); this difference was statistically significant (69 versus 32%; \( P < 0.005 \)) in bone lesions.

Only about one-third of the evaluable patients had estrogen receptors determined. Results regarding these patients are shown in Table 5. The difference in favor of the chemical endocrine arm was relevant in the group of estrogen receptor positive patients (80% with CMF plus T and 46% with CMF), but it should be noted that the number of receptor negative patients was too small for any comparative evaluation.

Median duration of objective remission was similar

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Median duration of objective remission was similar
in patients receiving chemotherapy alone (CMF; 47 weeks range, 16→135+) and in patients receiving the chemical endocrine therapy (CMF plus T; 51 weeks range, 12→191+; Fig. 2).

Hematologic and nonhematologic toxicity induced by cytotoxic agents included in the CMF regimen was relatively mild and not increased by the addition of T (Table 6). Side effects due to T were rare (Table 7). Hypercalcemia was documented in one patient at the beginning of treatment and reappeared when T was administered again after a withdrawal period. Only in this patient did side effects caused by T require a premature suspension of the drug.

An analysis of crossing of patients on chemotherapy alone (Group A) to second-line CMF plus T showed that nine patients were still treated with CMF. Twenty-one patients did not cross to CMF plus T or response to this regimen was not evaluable. For two patients, it was too early for the evaluation. Thus, 39 of 71 patients were evaluable. A number of clinical events, usually occurring in late advanced disease, brain metastases, nonevaluable sites of disease, death, etc., justifies the rather high number of untreated or nonevaluable cases. In the 39 evaluable patients treated with second-line CMF plus T, 12 showed objective remission with an overall response rate of 31% (Table 8). Seven patients had remission both to first-line CMF and to second-line CMF plus T, while five showed remission only to second-line CMF plus T. The median duration of objective remission in patients responding to second-line CMF plus T had not yet been reached after 55 weeks.

In patients of Group A, design of treatment, which was scheduled in two steps, offered a sequential possibility in achieving an objective response (to CMF and/or to CMF plus T). Figure 3 shows the actuarial time to treatment failure in all patients of each group, considering, in different curves, first-line CMF of Group A (median, 24 weeks), CMF followed by CMF plus T of Group A (median, 56 weeks), CMF plus T of Group B (median, 48 weeks). Differences between the first and the third curves (P = 0.06) and between the last two curves (P = 0.08) approach statistical significance.

Until now, a comparable number of patients on A and on B (29 of 71 and 31 of 62) received an Adriamycin-containing regimen after progression or relapse to treatments scheduled in the study.

Overall survival in the two treatment groups was longer in patients on CMF (Group A) than in patients on CMF plus T (Group B), considering both patients who entered (111 versus 78 weeks; Fig. 4) and those evaluable (118 versus 84 weeks). However, these differences were

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**Table 4. Objective Remission in Relation to Site of Metastases**

<table>
<thead>
<tr>
<th>Site of metastases</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMF</td>
</tr>
<tr>
<td>Soft tissue</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>Skin</td>
<td>15/25 (60%)</td>
</tr>
<tr>
<td>Nodes</td>
<td>19/30 (63%)</td>
</tr>
<tr>
<td>Viscera</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>4/10</td>
</tr>
<tr>
<td>Pleura</td>
<td>4/8</td>
</tr>
<tr>
<td>Liver</td>
<td>1/4</td>
</tr>
<tr>
<td>Abdominal masses</td>
<td>1/1</td>
</tr>
<tr>
<td>Bone</td>
<td>12/37* (32%)</td>
</tr>
</tbody>
</table>

*P < 0.005.

Pts: patients.

**Table 5. Objective Remission in Patients with Known Estrogen Receptor Status**

<table>
<thead>
<tr>
<th>Estrogen Receptor Status</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMF</td>
</tr>
<tr>
<td>Positive</td>
<td>6/13 (46%)</td>
</tr>
<tr>
<td>Negative</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Total</td>
<td>11/20 (55%)</td>
</tr>
</tbody>
</table>

Pts: patients.

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**Fig. 2. Duration of objective remission to first-line treatments. Differences are not statistically significant.**
**TABLE 6. Side Effects Due to Cytotoxic Chemotherapy**

<table>
<thead>
<tr>
<th>Side Effects (71 pts)</th>
<th>CMF (62 pts) %</th>
<th>CMF + T (62 pts) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white cell count*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4000</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>&lt;2500</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Platelet count*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120,000</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>&lt;75,000</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>Vomiting</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Loss of hair</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Cystitis</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Neurologic</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

* Blood cell count at day 1 and 8 of each cycle.

Pts: patients.

**TABLE 7. Side Effect Due to Tamoxifen**

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>CMF + T (62 pts) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>10</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>24</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td>Hypercalcemia induced</td>
<td>2</td>
</tr>
</tbody>
</table>

Pts: patients.

not statistically significant \((P = 0.25 \text{ and } 0.60 \text{ respectively})\).

Responding patients showed a longer median survival than nonresponding patients both in Group A (150 versus 76 weeks) and in Group B (110 versus 50 weeks). Differences between the two curves were statistically significant \((P < 0.02 \text{ and } <0.01, \text{ respectively})\). Patients not responding to CMF plus T (Group B) had a shorter median survival than patients not responding to CMF (Group A) (50 versus 76 weeks). The difference between the two curves was statistically significant \((P < 0.02)\) (Fig. 5).

**Discussion**

This prospective clinical trial has clearly shown that the response rate to a classical chemotherapy regimen (CMF) can be markedly and significantly increased by the concurrent addition of T. The additive effect seems to be optimal, since the increase in response rate to CMF due to T appears to be nearly of the same order as the usual response rate to T alone.\(^3\) Thus, the affirmation that a concurrent administration of hormonal and cytotoxic agents is irrational has been denied by this study. The increase in response rate due to T appears to be of an endocrine nature; in fact, it seems limited to estrogen receptor positive patients and shows a direct relationship to the duration of free interval.

The statistically significant advantages obtained by the concurrent chemical endocrine therapy when the dominant disease site was in bone should be interpreted. A pharmacologic influence on bone metabolism by T, independent of its antiproliferative activity, is improbable, as T alone does not appear to be selectively active on bone metastases.\(^3\) Conversely, remissions in bone lesions are generally difficult to evaluate. They usually require a rather long documentation period. Lytic bone parameters are usually not measurable for response, but only evaluable on the basis of their recalcification. For this reason, some therapeutic effects induced in bones either by chemotherapy or by endocrine therapy used as a single modality could possibly be classified as no change, i.e., no response. However, a number of subclinical therapeutic effects on this type of lesion could usefully be summed by the concurrent administration of chemical and endocrine agents.

It is rather disappointing that such a high remission rate as that obtained in our study by the concurrent chemical endocrine therapy does not correspond to any

**TABLE 8. Treatment with Second-Line CMF + T**

<table>
<thead>
<tr>
<th>Types of response</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of evaluable patients</td>
<td>39</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
</tr>
<tr>
<td>No change</td>
<td>13</td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (31%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>12 (31%)</td>
</tr>
</tbody>
</table>

**FIG. 3. Time to treatment failure in all patients considering, in Group A, both the first-line CMF and the first/second-line programs (CMF → CMF + T) and in Group B, the first-line program (CMF + T).**
increase in complete remission rate. This could be due to the usual difficulty in evaluating the completeness of response in breast cancer or to other unknown causes.

The increase in partial remission rate induced by the concurrent chemical endocrine treatment corresponds to an increase in time to treatment failure, but indeed it does not correspond to a significant increase either in duration of remission or in total survival. In designing our study, we preferred adding T to CMF rather than administering it alone at the time of progression or relapse. This experimental condition was aimed at assuring the exact evaluation of T activity only on tumor clones resistant to chemotherapy, re-emerging in sites of previous remission or emerging in new sites. At the same time, continuing chemotherapy had to assure a continuation of the remission of tumor clones which were still chemosensitive. By second-line CMF plus T, both new and repeated responses were seen. The new ones tended to decrease the difference in response rate between the two first-line treatments (CMF and CMF plus T), while the repeated ones tended to prolong the overall duration of remissions. Indeed, if the actuarial time to failure to both treatments scheduled in Group A (CMF and subsequently, CMF plus T) is taken into consideration, its total duration exceeds the duration of the time to failure to the first-line chemical-endocrine treatment. CMF and T do not appear to be cross resistant: treatment with the former does not preclude responsiveness to the latter. This is probably why survival was not prolonged by combining the chemical and endocrine therapies as first-line treatment. Indeed, the opposite seemed true.

Our results can be discussed in relation to those of other studies on the same subject. In this regard, only study designs comparing chemical (and not hormonal) treatments with chemical-hormonal ones should properly be taken into consideration. As regards remission rate, our study is the first detailed report to statistically demonstrate an advantage of a chemical endocrine treatment in comparison to the same chemical treatment. Interestingly, abstracts or preliminary results of two other studies showed advantages with tamoxifen added respectively to a combination of dibromodulcitol and Adriamycin or to CMF. If prednisone is considered as an endocrine therapy, it has to be observed that Band et al. showed advantages in response rate by adding this agent to CMF.

Other studies, however, fail to show any significant advantage using concurrent chemical and hormonal therapies in comparison to chemotherapy alone. In this regard, Brunner et al. tested ovariectomy or diethylstilbestrol or medroxyprogesterone added to a modified five-drug Cooper combination, Rubens et al. combined a progestogen (norethisterone acetate) to Adriamycin plus vincristine, Lloyd et al. added calusterone to Adriamycin plus cyclophosphamide, and Arraztoa and Ramirez used ovariectomy in premenopausal patients and tamoxifen in postmenopausal ones in comparison to CMF.
combination with 5-fluorouracil, Adriamycin and cyclophosphamide.

As regards duration of remission, our data differ from that reported by Lloyd et al.\textsuperscript{12} who found significant advantages with chemical-hormonal treatments in comparison to chemotherapy alone. However, other results showing no difference in duration of response are consistent with our data.\textsuperscript{9,10}

As regards survival, conflicting results abound, as some authors have reported significant advantages by chemical-hormonal treatment,\textsuperscript{11} some others a nonsignificant tendency in favor of the combined approach\textsuperscript{9} or no important differences\textsuperscript{13,20} and still others a trend towards a shorter duration of life by combined chemical-hormonal treatment in comparison to chemotherapy alone.\textsuperscript{10} We think that the design of these types of studies is fundamental and crucial in order to perform a comparative evaluation of survival. In fact, patients allocated to the chemotherapy arm could or could not receive the endocrine therapy included in the combined arm at the time of progression or relapse, or at any stage thereafter. As it seems unethical to deny a standard endocrine treatment to a subset of patients, it appears convenient that, after progression or relapse, the sequential administration of the same endocrine therapy included in the combined arm should be mandatory in the study design for the chemotherapy arm patients. Only in this way can possible differences in favor of the combined arm be considered as an advantage specifically due to the concurrent approach.

In conclusion, our study demonstrates that the combined chemical-endocrine regimen gives a significantly higher overall response rate than chemotherapy alone. It is possible that by combining other chemical and/or endocrine agents, the maximum plateau achieved so far with combination chemotherapy could be improved. Even though a high probability of obtaining and immediate objective response to a first-line treatment could be useful in situations urgently requiring a clinical response, our data suggest that the sequence of chemotherapy and endocrine therapy regimens (or possibly vice-versa) should be preferred for common clinical use. By using this sequence, a consecutive achievement of multiple responses becomes possible, and suggestions for the treatment of the last phase of the disease, i.e., administration or not of other endocrine regimens, may be obtained.

REFERENCES