Cyclophosphamide, Methotrexate, and Chronic Oral Tegafur Modulated by Folinic Acid in the Treatment of Patients with Advanced Breast Carcinoma

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BACKGROUND. Chronic oral tegafur (a 5-fluorouracil prodrug) modulated by folinic acid has antitumor activity in patients with metastatic breast carcinoma resistant to 5-fluorouracil or doxorubicin-based regimens. In this study, bolus 5-fluorouracil was substituted with chronic oral tegafur and folinic acid in a cyclophosphamide, methotrexate, and 5-fluorouracil-based regimen to study the activity of this novel regimen in patients with advanced breast carcinoma.

METHODS. This study was comprised of patients with advanced breast carcinoma and measurable or evaluable disease. Patients with prior chemotherapy were eligible. The regimen was comprised of cyclophosphamide, 600 mg/m^2, and methotrexate, 40 mg/m^2, both given intravenously on Day 1, and tegafur, 750 mg/m^2, with folinic acid, 45 mg/day, both given orally in 3 daily fractions on Days 2–14, every 3 weeks.

RESULTS. Forty-seven patients were included, 44 of whom were fully assessable. Three patients (7%) achieved a complete remission and 17 (38.6%) achieved a partial remission, for an objective response rate of 45.5% (95% confidence interval, 29–59%). The median duration of response was 11 months. In previously untreated patients the response rate was 54.5%. In patients previously treated with anthracycline or 5-fluorouracil-based regimens the response rates were 41% and 39%, respectively. Sixteen patients (36.4%) had disease stabilization. The median overall time to progression was 10 months. Toxicities usually were mild and were comprised of leukocytopenia, mucositis, emesis, and diarrhea.

CONCLUSIONS. Chronic oral tegafur and folinic acid combined with intravenous cyclophosphamide and methotrexate at the dose and schedule used in the current study has significant antitumor activity both as first-line chemotherapy as well as in other patients with advanced breast carcinoma who had prior chemotherapy. This regimen is well tolerated, with gastrointestinal toxicity being the most frequent and dose-limiting toxicity. ***Cancer* 1998;82:878–85.** © *1998 American Cancer Society.*

KEYWORDS: breast carcinoma, tegafur, folinic acid, biochemical modulation.

Tegafur (ftorafur), a tetrahydro-2-furanyl derivate of 5-fluorouracil (5-FU), is an antimetabolite with activity against metastatic breast carcinoma when given as a single agent.[1] In addition, we reported previously that chronic oral tegafur and folinic acid was well tolerated in heavily pretreated metastatic breast carcinoma patients and was active in women previously exposed to 5-FU and/or anthracyclines.[2] In the current trial we sought to investigate the antitumor activity of oral tegafur and folinic acid in combination with cyclophosphamide and methotrexate (CMFt-FA) in patients with advanced breast carcinoma.

The cyclophosphamide, methotrexate, and 5-FU (CmF)-based regimens are used widely for the treatment of breast carcinoma, both

in the metastatic and adjuvant setting.[3,4] In the CMF regimens, 5-FU is given as a short bolus infusion and has a very short plasma half-life (4.5–13 minutes).[5–8] Because 5-FU is a S-phase specific inhibitor of the enzyme thymidylate synthase,[5–8] prolonged exposure of tumor cells to this drug may be more effective than a rapid administration. Supporting the clinical benefit of prolonged 5-FU treatment compared with short bolus infusion, a randomized trial in patients with colorectal carcinoma demonstrated that continuous infusional 5-FU for 10 weeks achieved a significant higher response rate than a 5-day bolus treatment (30% vs. 7%).[9] Another way to increase the activity of 5-FU is by adding folinic acid. Folinic acid increases the stability of the ternary complex between fluorodeoxyuridylate (a by-product of 5-FU), 5,10-methylenetetrahydrofolate, and thymidylate synthase, resulting in a greater enzyme inhibition and significant improvement in tumor cell killing on a dose-dependent and duration of exposure-dependent manner.[5,8,10,11] 5-FU plus folinic acid has been shown to be more active than 5-FU alone in the treatment of patients with advanced colorectal carcinoma,[12–14] and a meta-analysis has shown that this combination increases the survival of patients with Dukes stage B and C colon carcinoma.[15] In breast carcinoma, 5-FU and folinic acid is active in heavily pretreated patients, both alone[16–18] and as a part of a combination treatment.[19–23] Reported response rates to 5-FU plus folinic acid range from 24–60% in breast carcinoma patients who had prior chemotherapy.[16,22,28] This activity appears to be higher than treatment with 5-FU alone,[3,24] although direct comparisons are not available.

Tegafur is hydroxylated and converted to 5-FU in vivo by hepatic microsomal enzymes.[25] Oral administration of tegafur in divided doses simulates a continuous infusion of 5-FU and therefore this prodrug has the potential to be an alternative to prolonged intravenous infusions of 5-FU.[1,26,27] A Phase II trial with oral tegafur in previously treated metastatic breast carcinoma patients provided an overall response rate of 29%.[1] This level of activity is in the range of efficacy reported with continuous infusion 5-FU.[7,28] Furthermore, we reported significant activity of chronic oral tegafur and folinic acid in a Phase II trial in metastatic breast carcinoma patients who had prior chemotherapy, with a response rate of 32% (95% confidence interval [CI], 23–41%).[2] The toxicity of the regimen was mild, and significant myelossuppresion was not observed.[2] These characteristics led us to incorporate tegafur-folinic acid as part of a novel CMF-based regimen comprised of intravenous cyclophosphamide and methotrexate and oral tegafur and folinic acid. Our findings indicate that the studied chronic oral tegafur and folinic acid-containing CMF regimen is active and has a manageable toxicity profile.

PATIENTS AND METHODS

Patients

Eligibility criteria were histologically proven locally advanced or metastatic breast carcinoma (American Joint Committee on Cancer Stages IIIB and IV-T4 N1-3 M0 and M1)[29] and measurable or evaluable disease. Patients with only serosal effusions, bone metastases (except lytic bone metastases measurable by computed tomography scanning or magnetic resonance imaging), or elevated CA 15.3 levels were considered evaluable. Patients also were required to be age > 18 years and physiologic age < 75 years; have a Karnofsky performance status (KPS) of $\geq 60\%$, have discontinued of chemotherapy at least 4 weeks before study entry (6 weeks if previous treatment was with mitomycin C); no radiotherapy in the sites of measurable disease in the past 4 weeks; recovery from toxic effects of any prior chemotherapy; creatinine level ≤ 2 mg/dL; serum bilirubin ≤ 2 mg/dL; and leukocyte count $> 3.5 \times 10^9$/L, absolute neutrophil count $> 1.5 \times 10^9$/L, and platelet count $> 100 \times 10^9$/L.

Patients with brain metastases were eligible if they had received radiation treatment with disease control or were undergoing radiotherapy, and they had other evaluable or measurable lesions. Patients with carcinomatous meningitis, a history of malignancy other than breast carcinoma (except basal cell or squamous cell carcinoma of the skin), significant previous cardiomyopathy, active infectious disease, and/or who were pregnant or lactating were ineligible. Oral informed consent was obtained from all patients.

Treatment

The regimen, which was administered on an outpatient basis, was comprised of intravenous cyclophosphamide, 600 mg/m^2, and methotrexate, 40 mg/m^2 on Day 1, and tegafur, 750 mg/m^2/day with folinic acid at 45 mg/day, both given orally in 3 daily fractions on Days 2–14 every 3 weeks (CMFt-FA). Because tegafur capsules contain 400 mg of tegafur, daily doses were rounded to the nearest multiple according to body surface area. For this trial, tegafur was purchased from Laboratorios Almirall (Utefos, Laboratorios Almirall, Barcelona, Spain). This drug currently is unavailable in the U. S. and Canada. However, it is available commercially in several countries: Italy (Lusofarma-Farmasines); Germany and Israel (Pfizer Inc.); Sweden, Norway, and Denmark (Orion-Farmos Corporation); several eastern European countries (Medesport); and Japan (Takio). Antiemetic therapy was comprised of intravenous ondansetron, 8 mg, and dexamethasone,

20 mg, on the day of cyclophosphamide and methotrexate administration, followed by oral metoclopramide, 0.5 mg/kg, 3 times daily for 3 days. Patients were treated until tumor progression or unacceptable toxicity. Patients achieving a tumor response with CMFt-FA were allowed to be considered for high dose chemotherapy if they fulfilled the institutional guidelines. Patients treated for Stage IIIB disease were evaluated for resectability after four cycles, at which time they underwent surgical resection or locoregional radiotherapy. Patients with an objective response after surgery received two postsurgical cycles of CMFt-FA.

Assessment of Results

All patients were evaluable for toxicity and those receiving one full cycle were evaluable for response. Tumor response was evaluated every three cycles or earlier if clinically indicated. A complete response (CR) was defined as the disappearance of all physical and radiographic evidence of the tumor during at least a 4-week period. Partial response (PR) was defined as a $\geq$50% decrease in the sum of the products of the perpendicular dimensions of all measurable lesions lasting at least 4 weeks. Progressive disease was defined as an increase in size $<$ 25% in any measurable lesion or the appearance of new lesions. Patients not showing these characteristics were defined as having stable disease. Response designations for bone disease were: CR: disappearance of all objective and clinical disease, including complete normalization of bone scans and radiographs; PR: lytic lesions, unequivocal recalcification, on plain films that lasted at least 2 months without appearance of new lesions or increase in size of previously recorded lesions (PR was not considered in nonmeasurable bone metastases); and progressive disease, defined as worsening of scans and/or X-rays performed after 9 weeks of treatment.

Toxicity was recorded on a 3 week basis at the time of administration of the intravenous chemotherapy using the National Cancer Institute common toxicity criteria.[30] Dose reductions were as follows. In patients experiencing Grade 1-2 hematologic toxicity the dose of cyclophosphamide was reduced by 25% only in case of reappearance of Grade 2 toxicity in subsequent cycles. In patients developing Grade 3 hematologic toxicity, therapy was discontinued until recovery from toxicity and the dose of cyclophosphamide and methotrexate was reduced by 25% in subsequent cycles. In case of Grade 4 hematologic toxicity, treatment was restarted after full hematologic recovery at 50% of the original doses. Grade 1-2 gastrointestinal toxicity was managed with symptomatic treatment and restarting tegafur-folinic acid at 66% of the original doses after recovery from toxicity, and this dose was maintained in subsequent cycles. Patients with Grade 3-4 gastrointestinal toxicity received symptomatic treatment and tegafur-folinic acid were reintroduced at 33% of the previous doses 1 week after complete recovery from toxicity. In any case, patients with recurrence of Grade 3-4 toxicity after dose reduction were removed from the study. Grade 2-4 skin toxicity was managed with tegafur-folinic acid withdrawal until full recovery and reintroduction at 66% of the previous dose. Patients with unacceptable toxicity (defined as recurrence of Grade 3-4 toxicity after dose reductions) were withdrawn from the protocol.

TABLE 1
Pretreatment Characteristics

	No.	%
No. of patients	47	
Age (yrs) median (range)	55 (29–77)	
Gender		
Female	46	98%
Male	1	2%
Karnofsky index, median % (range)	80 (60–100)	
Menopausal status		
Premenopausal	12	26%
Postmenopausal	34	74%
No. of patients with prior endocrine therapy	23	49%
Adjuvant only	10	21%
Advanced or metastatic only	8	17%
Both adjuvant and metastatic	5	11%
No. of patients with prior chemotherapy	36	77%
Adjuvant only	14	30%
Advanced or metastatic only	13	28%
Both adjuvant and metastatic	9	19%
5-FU-containing	36	77%
Anthracycline-containing	31	66%
Predominant disease sites		
Locally advanced	4	9%
Visceral	26	55%
Soft tissue and bone	17	36%

5-FU: 5-fluorouracil.

Statistical Methods

Duration of response and time to progression were calculated from the date of initiation of therapy until progression or last clinical visit. Survival was calculated from the date of initiation of therapy until death. Median survival, median time to progression, and median response durations were estimated using the Kaplan–Meier method.[31]

RESULTS

From February 1995 to October 1995, 47 patients were entered on the study. The median follow-up period was 15 months (range, 13–21+ months). Patient characteristics are shown in Table 1. Most patients pre-

TABLE 2
Response to CMFt-FA

	No. of patients	Total evaluable	%
Complete response	3	44	7%
Partial response	17	44	38.6%
Stable disease	16	44	36.4%
Progression	8	44	18%
Overall response rates			
Whole group	20	44	45.5%
First-line chemotherapy	12	22	54.5%
5-FU-pretreated	13	33	39%
Anthracycline-pretreated	12	29	41%

CMFt-FA: oral tegafur and folinic acid combined with cyclophosphamide and methotrexate; 5-FU: 5-fluorouracil.

viously had been exposed to chemotherapy, either in the adjuvant setting (14 patients), for advanced or metastatic disease (13 patients), or both (9 patients). Only 11 patients (23%) had not received prior chemotherapy. Thirty-six patients (77%) had received previous 5-FU-containing regimens, and 31 (66%) had received previous anthracycline-containing regimens. In terms of dominant disease sites, the majority of patients had visceral-dominant metastatic disease (55%), and 33 patients (70%) had >1 disease site. The median number of involved organs was two (range, one to five). Forty-five patients (96%) had measurable disease and the remaining 2 patients (4%) had bone metastases evaluable by bone scan.

Efficacy

The median number of cycles of therapy administered was 7 (range, 1–18+ cycles), with a total number of 348 cycles. Two patients did not complete the first cycle of therapy, one due to cerebral hemorrhage resulting in death and one due to Grade 3 emesis that recurred after the reintroduction of tegafur and folinic acid. One patient with brain, bone, and lymph node metastases received two cycles of therapy, discontinued the treatment voluntarily, and refused to undergo studies to assess response. These three patients thus were considered ineligible for efficacy analysis, but they were considered evaluable for toxicity assessment and were included in the actuarial survival curve. Response rates for the 44 evaluable patients are shown in Table 2. The overall response rate was 45.5% (95% CI, 29–59%), with 3 CRs and 17 PRs. Response rate for patients receiving CMFt-FA as the first-line chemotherapeutic regimen was 54.5% (12 of 22 evaluable patients; 95% CI, 33.5–75.5%). Thirteen of 33 evaluable patients previously treated with bolus 5-FU-containing regimens responded (39%; 95% CI, 22.5–55.5%). Disease stabilization was observed in 15 of the 5-FU pretreated patients (45.5%), and only 5 evaluable patients previously treated with bolus 5-FU progressed to CMFt-FA. Twelve of 29 patients previously exposed to anthracycline-based regimens responded to therapy (41%; 95% CI, 23–59%). Five of these 12 patients who responded to CMFt-FA were entered onto the protocol while in progression during an anthracycline-containing regimen. The median overall duration of response was 11 months (range, 3–21+ months). Characteristics of responding patients are outlined in Table 3.

Other than CR or PR, 16 patients (36.4%; 95% CI, 22.5–50.5%) had disease stabilization, some of prolonged duration (median duration of stabilization, 9 months; range, 2–14+ months). Thirty-six of the 44 evaluable patients were off-study at the time of analysis (22 because of disease progression, 3 for toxicity, 1 due to death from an unrelated cause [thromboembolic episode]), and 10 patients were switched to other regimens. Three of these ten patients underwent high dose chemotherapy with peripheral stem cell support after a major PR to CMFt-FA, and four received tamoxifen treatment [one on PR and three with stable disease after more than seven cycles of chemotherapy]. The other three patients were treated for Stage III breast carcinoma. Of these, two underwent surgery and radiotherapy followed by two cycles of CMFt-FA, and one previously treated with radiotherapy was considered to have unresectable disease and was switched to tamoxifen. At the time of survival analysis, median survival was not yet reached, and median time to progression was 10 months. The 1-year actuarial percentage of survival was 74%, and the 1-year actuarial percentage of patients free of disease progression was 47%.

Toxicity

Toxicity is outlined in Table 4. The main toxicities were leukocytopenia, emesis, mucositis, and diarrhea. Grade 3-4 toxicities were infrequent, the most common being emesis. Three patients were withdrawn from treatment due to toxicity: one because of a Grade 3 urticariform reaction while receiving treatment that recurred after restarting tegafur-folinic acid; one for recurrent Grade 2 emesis after dose reduction of tegafur and folinic acid; and one patient who was hospitalized for Grade 3 diarrhea and Grade 2 emesis while receiving tegafur and folinic acid at 66% of the original dose. No other patient required hospitalization for toxicity. Hematologic toxicity was comprised mainly of leukocytopenia, which was the cause for dose delays in 11 cycles. Other causes of dose delays were emesis

TABLE 3
Characteristics of Patients who Responded to CMFt-FA

Patient no.	Response	Disease sites	Prior therapy	Response duration (mos)
1	CR	Lymph nodes	aFAC	21+
2	CR	Breast, lymph nodes, liver		17+
3	CR	Lymph nodes	aFAC, aTMX	16+
4	PR	Lymph nodes, bone	aCMF	19+
5	PR	Breast, lymph nodes, skin	FEC	18+
6	PR	Lung, pleura	aTMX, FEC	17+
7	PR	Breast, lymph nodes, lung, pleura		16+
8	PR	Breast		16+
9	PR	Breast, lymph nodes		13+
10	PR	Breast, lymph nodes	aFAC, aTMX	12
11	PR	Breast bone	FEC	12
12	PR	Breast, lymph nodes, bone, lung	aFEC, aTMX, MP	10
13	PR	Lung	aFAC, aTMX	9
14	PR	Lymph nodes, bone	aTMX, MP, Form	7
15	PR	Breast, bone	FEC	6
16	PR	Breast, lung		6
17	PR	Breast, lymph nodes		6
18	PR	Lymph nodes, bone, pleura	TMX, FAC	4
19	PR	Bone	aCMF	4
20	PR	Breast, lymph nodes	TMX, FEC, VNR	3

Oral tegafur and folinic acid combined with cyclophosphamide and methotrexate; CR: complete response; PR: partial response; aFAC: adjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide; aTMX: adjuvant tamoxifen; aCMF: adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil; MP: medroxyprogesterone; FEC: 5-fluorouracil, epirubicin, and cyclophosphamide; TMX: tamoxifen; VNR: vinorelbine; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; Form: formestane.

TABLE 4
Number of Patients with Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytopenia	2 (4%)	9 (19%)	1 (2%)	—
Thrombocytopenia	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Anemia	4 (8%)	2 (4%)	2 (4%)	—
Mucositis	10 (21%)	5 (10.6%)	1 (2%)	—
Diarrhea	7 (14.9%)	5 (10.6%)	2 (4%)	—
Nausea/emesis	7 (14.9%)	17 (36%)	3 (6%)	—
Epigastric Pain	3 (6%)	2 (4%)	1 (2%)	—
Skin	—	1 (2%)	1 (2%)	—
Alopecia	6 (12.8%)	2 (4%)	—	—
Fever	—	1 (2%)	—	—
Conjunctivitis	1 (2%)	—	—	—

(one cycle), diarrhea (one cycle), fever without documented infection (one cycle), and Grade 4 thrombocytopenia (one cycle). Twenty-two of the patients (47%) required a 33% reduction in tegafur-folinic acid dose. Dose reductions mainly were due to diarrhea, and appeared to be more frequent after patients received several cycles of treatment, because 60% of the dose reductions began when the patient already had received six cycles of therapy. In most cases, recurrence of Grade 2-3 toxicity was avoided with dose reductions in subsequent cycles. Cyclophosphamide dose reductions were required in 21 cycles (6%), with the main cause being leukocytopenia. Methotrexate was administered at 75% of the planned doses in 11 cycles because of leukocytopenia and thrombocytopenia. One patient developed Grade 2 skin toxicity consistent with a tegafur-related hand-foot syndrome. The patient also had persistent Grade 2 diarrhea and mucositis, but was able to continue treatment at 66% of the dose of tegafur-folinic acid. Two patients died during treatment. The first patient died as a consequence of a cerebral hemorrhage during the first cycle of therapy. The patient had normal platelet counts and therefore this was believed to be unrelated to therapy. Another patient died of a pulmonary thromboembolism after five cycles of therapy after having achieved a PR.

DISCUSSION

In our prior Phase II trial of oral tegafur plus folinic acid in previously treated metastatic breast carcinoma patients the response rate was 32%.[2] Although not directly comparable, with the incorporation of cyclophosphamide and methotrexate to the tegafur-folinic acid combination the response rate in the present trial increased to 45.5%. This included a remarkably high rate of responses in patients previously treated with anthracyclines (41%) and 5-FU (39%).

The encouraging activity observed with tegafur

may be related to the fact that its oral chronic administration results in the achievement of continuous optimal levels of 5-FU both in the plasma and in the tumor.[1,26,27,32] There is strong evidence that prolonged 5-FU exposure may be more advantageous than shorter infusions. In vitro data[5,6] and studies in patients with metastatic colon carcinoma[33,34] suggest that a protracted infusion of 5-FU is able to overcome resistance to pulsed 5-FU. Also, UFT (a combination of tegafur and uracil at a molar ratio of 1:4) at similar doses as those used in our trial has been shown to produce higher 5-FU concentrations in metastatic lymph nodes from breast carcinoma patients compared with nonaffected lymph nodes.[32] Continuous infusion of fluoropyrimydines (with and without folinic acid modulation) is the mainstream of several other combination treatment regimens for advanced and metastatic breast carcinoma. In most of these studies, response rates have been in the high range of what would have been expected using bolus 5-FU.[7,20–22,35]

In our study folinic acid was added to tegafur to further enhance its antitumor activity. Preclinical data have shown that prolonged infusions of folinic acid are necessary to maximize the slow cellular uptake of reduced folates,[10] and can overcome partially the resistance to 5-FU in cancer cells that have low intracellular concentrations of reduced folates.[36] Oral administration of folinic acid appears to yield results similar to those obtained intravenously,[37] and may even have some advantages in addition to patient convenience. The levels of folinic acid obtained by oral administration in divided doses are comparable to the intravenous route and simulates a continuous intravenous infusion. In animal models and in pharmacologic studies, oral administration of folinic acid has been shown to have a preferential absorption of the l-isomer over the d-isomer, the latter being biologically inactive and considered to be the cause of several undesirable effects with the intravenous administration of folinic acid.[5,36,38]

Based on our prior Phase II trial with tegafur in combination with folinic acid,[2] the current protocol included a 33% dose reduction of these 2 drugs in case of Grade 1-2 mucositis, diarrhea, and/or nausea and emesis to favor compliance to the protocol. The addition of cyclophosphamide and methotrexate did not appear to increase the gastrointestinal toxicities of the tegafur-folinic acid combination. Although no hematologic toxicity was noted with the use of tegafur and folinic acid alone,[2] we observed hematologic toxicity with the CMFt-FA regimen. However, there were no episodes of neutropenic fever or requirements for transfusion of blood products. Also, a low but significant percentage of patients developed Grade 1-2 alopecia, which was not observed in the previous trial. Other toxicities were comparable, with the most frequent side effects being nausea/emesis, mucositis, and diarrhea. These side effects are similar to those reported with continuous 5-FU infusion. In published series, continuous 5-FU therapy resulted in less myelosuppression than rapid bolus administration, although mucositis and diarrhea appear to be more common and severe than in similar regimens with bolus fluoropyrimidines.[16,20–22,35,39] Moreover, a new toxic reaction has emerged with prolonged continuous infusion of fluoropyrimidines: palmar-plantar erythrodysesthesia.[2,7,22,40] However, overall toxic reactions are not greater than with bolus 5-FU administration, and the decrease in myelotoxicity allows for a two- to fivefold dose increase in fluoropyrimidines with the continuous administration protocols.[21]

The activity and manageability of tegafur-folinic acid incorporated into the CMF combination regimen warrants further clinical development of the use of oral tegafur in combination with other highly active agents in breast carcinoma, such as taxanes. In this regard, a Phase II trial of tegafur and folinic acid administered orally for 13 days after a 3-hour infusion of paclitaxel in anthracycline-pretreated metastatic breast carcinoma patients currently is active in our institution. The observed toxicity profile, with nonsignificant myelossuppresion, also suggests that tegafur plus folinic acid could be incorporated with other myelosuppressive agents, in addition to taxanes. Furthermore, it also may be a useful agent in those situations in which there is limited bone marrow reserve (i.e., in patients with metastatic breast carcinoma who recur after high dose chemotherapy with peripheral stem cell support).

This modified CMF regimen is well tolerated and active in patients with advanced and metastatic breast carcinoma, with a high response rate in anthracycline-pretreated patients and in patients previously treated with bolus 5-FU-containing regimens. The oral administration of tegafur allows for the continuous exposure to 5-FU while avoiding the inconveniences of continuous infusion of 5-FU. Thus, in the setting of metastatic breast carcinoma, in which palliation and quality of life are important goals, the CMFt-FA regimen may offer a convenient, albeit active, treatment alternative.

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