Phase II Trial of an All-Oral Regimen of Tegafur and Folinic Acid in Patients with Previously Treated Metastatic Breast Cancer

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Background. **Tegafur is an antimetabolite slowly metabolized to 5-fluorouracil in vivo. Protracted administration of oral tegafur is active in metastatic breast cancer, with reported response rates ranging from 29 to 44%. The addition of folinic acid could improve the efficacy of tegafur by means of biochemical modulation.**

Methods. **A prospective Phase II trial in patients with pretreated metastatic breast cancer was performed. The regimen consisted of oral tegafur (750 mg/m^2/day) and oral folinic acid (45 mg/day) for 21 days, recycling at day 28.**

Results. **Twenty-five patients were included. Eight partial responses were observed for an objective response rate of 32% (95% confidence intervals for response, 23–41%). The median duration of response was 7 months. According to WHO criteria, 24% of patients experienced grade 3 mucositis and 12% grade 3 diarrhea, but no other significant toxicities were observed. Twenty-eight percent of patients required dose reductions for toxicity.**

Conclusions. **A significant response rate with oral tegafur and folinic acid in patients with heavily pretreated breast cancer was found. This all-oral regimen, which could be safely administered on an outpatient basis, deserves further evaluation to define the role of folinic acid on the activity of tegafur in metastatic breast cancer. *Cancer* 1995;75:831–5.**

Key words: breast cancer, biochemical modulation, tegafur, leucovorin.

Introduction

The main objectives of conventional chemotherapy for metastatic breast cancer are palliation and control of disease. Patients relapsing after initial chemotherapy have progressively lower response rates and briefer duration of responses to successive regimens. There is a need to provide good palliative regimens for these patients. Therefore, the availability of an active oral regimen could be of great interest.

Tegafur (ftorafur) is a fluoropyrimidine that is slowly metabolized to 5-fluorouracil (5-FU) in vivo.[1,2] Protracted administration of oral tegafur comes closest to reproducing the pharmacokinetics of the true 5-FU infusions.[2,3] The activity of oral tegafur alone has been shown in 5-FU–sensitive neoplasms.[4–7] Reported response rates in metastatic breast cancer range from 29% to 44%.[6–9]

Biochemical modulation of tegafur by oral folinic acid is an attractive approach to increase its efficacy.[10,11] Furthermore, oral administration of folinic acid may have some pharmacokinetic advantages and repeated low doses of folinic acid could provide enough concentration to modulate the action of 5-FU.[12,13] A concentration of folinic acid of 1 micromol/l seems to be enough to achieve an effective modulation of 5-FU, and can be reached at doses of 25 mg orally every 8 hours.[13,14]

Several reports[15–18] have shown high response rates with 5-FU modulated by folinic acid as second-line chemotherapy in metastatic breast cancer. Swain et al.[16] showed that the addition of folinic acid increases stabilization of the 5-fluorodeoxyuridylate-thymylidate synthase-folate ternary complex in human breast cancers in vivo, and a higher level of enzyme inhibition in patients who responded compared with those who had progressive disease.

The modulatory antitumoral activity of folinic acid on tegafur has been shown in animal models.[19] A Phase I study with a fixed schedule of oral tegafur (750 mg/

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m^2/day for 21 days) and increasing doses of folinic acid showed a statistically significant linear correlation between folinic acid dose and toxicity. Dose-limiting toxicities were mucositis and diarrhea. The recommended dose for Phase II studies was 45–60 mg/day of folinic acid and tegafur 750 mg/m^2/day.[20] Other studies suggest that higher doses could be administered.[21–22] Nevertheless, 5-FU plus low dose folinic acid appears to have at least the same activity than 5-FU plus high dose folinic acid in advanced colorectal cancer,[23,24] and the infusion of 5 mg/m^2/day of folinic acid seems to result in biochemical modulation of protracted continuous infusion of 5-FU.[25] Therefore, we chose the dose suggested in the aforementioned Phase I trial.[20]

The main advantage of an all-oral regimen of biochemical modulation expected was avoiding the need for frequent administration of intravenous treatment associated with the use of 5-FU and folinic acid. For these reasons, we conducted a Phase II study of oral tegafur and folinic acid in patients with previously treated metastatic breast cancer.

Patients and Methods

Eligibility criteria were: histologically proven carcinoma of the breast; presence of metastases; age older than 18 years and a physiologic age younger than 70 years; predicted life expectancy of at least 12 weeks; Karnofsky performance status of 60% or greater; measurable disease; previous exposure to at least one standard systemic chemotherapy; discontinuation of chemotherapy at least 4 weeks before our study; recovery from the toxic effects of that previous treatment; adequate renal function manifested by a creatinine level of no greater than 1.5 mg/dl; adequate hepatic function (serum bilirubin of no greater than 1.5 mg/dl); and bone marrow reserve (leukocyte count $> 4 \times 10^9$/l and platelet count $> 100 \times 10^9$/l).

Patients with brain metastasis, carcinomatous meningitis, symptomatic lymphangitic pulmonary metastases, bone-only disease, history of malignancy (except basal cell or squamous cell carcinoma of the skin), and/or other serious medical illnesses and patients unable to tolerate or implement oral therapy were ineligible. All patients gave oral informed consent.

Therapeutic Plan

The treatment, which was administered on an outpatient basis, consisted of oral tegafur 750 mg/m^2/day (capsules contain 400 mg of tegafur, so daily doses were rounded to the nearest multiple according to body surface area) and folinic acid 45 mg/day, both given orally in three daily fractions for 21 days, recycling at day 28. Patients experiencing grade I–II toxicity received symptomatic treatment, and the dose of both agents was reduced by 33% only in case of reappearance of grade II toxicity in subsequent cycles. In patients developing grade III–IV toxicity, therapy was discontinued and the dose of both agents was reduced by 33% in subsequent cycles. Patients with grade III toxicity after dose reduction were removed from the study. Patients were treated until the occurrence of tumor progression or unacceptable toxicity.

Assessment of Results

All patients receiving one cycle were considered evaluable for response and toxicity. Response in patients with measurable disease on physical examination was evaluated after each cycle. Other tests to evaluate response were performed every two or three cycles. Response and toxicity were recorded according to the WHO recommendations.[26] A complete response was defined as the disappearance of all physical and radiographic evidence of the tumor during at least a 4-week period. Partial response was defined as a decrease in the products of the largest dimensions of measurable lesions by greater than 50%, no new lesions, or progression of other disease sites, during at least 4 weeks. Progressive disease was defined as an increase in size greater than 25% of the sum of the products of diameters of the measurable lesions or the appearance of new lesions. Patients not showing these characteristics were defined as having stable disease. Toxicity was recorded on a monthly basis.

Statistical Methods

Duration of response and time to progression were calculated from the data 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.[27] Therapeutic responses were observed in the first 14 patients, so we extended patient accrual to 25.

Results

From October 1992 to October 1993, 25 assessable patients were included. The median follow-up was 8 months (range, 2–12+ months). Patient characteristics are shown in Table 1. The median number of cycles of therapy administered was 6 (range, 1–12 cycles), with a total number of 144 cycles. All patients had received at least one previous chemotherapy treatment, with a median number of previous chemotherapy regimens of 3 (range, 1–6 regimens); 24 patients had received previ-

Table 1. Pretreatment Characteristics of Evaluable Patients

No. of patients	25
Median age, yr (range)	55 (37–71)
Karnofsky index	
60–70	8
80–100	17
No. of patients with prior chemotherapy	25
5-Fluorouracil-containing	24
Doxorubicin-containing	21
Adjuvant chemotherapy	14
Chemotherapy for metastatic disease	25
Median no. of prior chemotherapy regimens (range	
Overall	3 (1–6)
Metastatic disease	2 (1–6)
No. of patients with prior endocrine therapy (range)	14 (0–2)
Median no. of metastatic sites (range)	2 (1–6)
No. of sites of metastatic disease	
Skin/soft tissue	12
Bone	12
Nodal	10
Lung	7
Breast	5
Pleura	4
Liver	4
Pericardium	1

ous 5-FU containing-regimens and 21 had received previous doxorubicin-containing regimens.

Therapeutic Responses

Response rates are shown in Table 2. The overall response rate was 32% (95% exact confidence intervals, 23–41%), with 8 partial responses out of 25 patients. The mean number of cycles to achieve a partial response was two (range, 1–3 cycles). Median duration of partial responses was 7 months (3–10+ months). Characteristics of responding patients are outlined in Table 3. Responses were seen in skin/soft tissue, lymph node, bone, breast, lung, and pleura.

Other than partial responses, 12 patients (48%; 95% confidence interval, 29–67%) had disease stabilization, some of prolonged duration (median duration of stabilization 6 months, range 2–12+ months). At the time of analysis, 18 patients were excluded from protocol (17 because of disease progression, 11 who were alive and 6 who died; 1 because of toxicity) and 7 were still on treatment (either in partial response or stabilization).

Median survival was not reached, and median time to progression was 9 months. The 1-year actuarial percentage of survival was 63%, and the 1-year actuarial percentage of patients free of progression was 10%.

Toxicity

Toxicity is outlined in Table 4. The main toxicities were mucositis and diarrhea; 24% of patients experienced grade 3 mucositis and 12% grade 3 diarrhea. Only one patient was hospitalized for grade 4 mucositis; no other patient was admitted for toxicity. Dose reductions were required in 28% of patients. In most cases, grade III toxicity was avoided with dose reductions in subsequent cycles (Table 5). Other gastrointestinal toxicities, such as nausea and vomiting, epigastric pain, or anorexia, were observed less frequently and were easily manageable. These toxicities usually appeared during the third week of therapy. One patient developed hand–foot syndrome after two cycles of therapy and was the only patient removed for toxicity. Hematologic toxicity was extremely low. Two patients had an increase in serum bilirubin after two cycles without evidence of liver disease; bilirubin became normal after dose reduction. No patient developed neurologic toxicity or alopecia.

Discussion

Our results suggest the feasibility of an all-oral regimen with tegafur and folinic acid in patients with heavily pretreated metastatic breast cancer. Considering the very advanced stage of our patients the response rate of 32% is noteworthy. This fact is reflected by the number of previous chemotherapy regimens and by the number of disease sites (Table 1). Specifically, almost all patients had received previous 5-FU (24 patients out of 25) and doxorubicin (21 patients out of 25). Most responses were achieved in nonvisceral sites, which parallels the response profile observed with other chemotherapeutic drugs. Of note, the median duration of response was 7 months. An additional 48% of patients experienced disease stabilization having a median time to progression of 6 months. Overall, a very high proportion of patients achieved disease control of meaningful duration given the palliative nature of chemotherapy in this setting, resembling the activity of other second-line regimens tested in our unit.[28,29]

The activity of tegafur alone in metastatic breast

Table 2. Response to Tegafur + Folinic Acid

Response	Patients
CR	0 (0)
PR	8 (32)
SD	12 (48)
PD	5 (20)

CR: complete response; PR: partial response; SD: stable disease; PD: progression.
Values are no. (%).

Table 3. Characteristics of Patients Who Had a Response

Patient no.	Metastatic sites	Prior chemotherapy	Response duration (mo)	No. of cycles to PR
1	Node	CMF, FAC	PR (4+)	2
2	Skin, breast	FAC, CMF, MV	PR (5)	2
3	Node, breast, bone	AC	PR (10+)	2
4	Node, bone	FAC, CMF	PR (9+)	3
5	Node, lung	aCMF, CMF, MY	PR (9)	1
6	Skin	aCMF, FAC	PR (3)	1
7	Skin, pleura, bone	aCMF, FAC	PR (5+)	2
8	Skin	AC	PR (6)	2

CMF: cyclophosphamide, methotrexate, fluorouracil; PR: partial response; FAC: fluorouracil, doxorubicin, cyclophosphamide; MV: mitomycin, vinblastine; aCMF: adjuvant CMF.

cancer has been described in several trials. A Phase I–II trial of tegafur performed by Ansfield et al.[6] showed a 44% response rate in women with advanced breast cancer, but included low numbers of patients. In a review of the activity reported in Phase II trials for all cytotoxic drugs introduced into clinical trial by the National Cancer Institute between 1970 and 1985, Marsoni et al.[7] identified tegafur as an active drug in breast cancer with a response rate of 37% (80% confidence interval, 30% to 45%). A review of the Japanese experience with tegafur in breast cancer has shown a high number of responses (response rate also of 37%).[8] Recently, Kajanti et al.[9] reported a Phase II trial of oral tegafur alone in metastatic breast cancer achieving a 29% response rate in 21 evaluable patients. Although our response rate is not much higher, it should be noted that their patients were significantly less pretreated than ours, with a median number of previous chemotherapeutic regimens of 2 (range, 0–4 regimens), and only 13 of 21 (61%) patients were previously exposed to 5-FU. Thus, the reported response rates in our trial may be significantly lower of what may be achieved in a less heavily pretreated population, and tegafur plus folinic acid might well be better than tegafur alone taking into account the characteristics of our patients.

Moreover, the degree of activity is quite similar to that achieved in patients with previously treated metastatic breast cancer receiving 5-FU and folinic acid.[15–18] Several trials have evaluated the biochemical modulation of 5-FU with folinic acid in metastatic breast cancer, and response rates ranged from 17% to 48%, and their activity seems partly related to the degree of previous exposure to chemotherapy. The activity has been greater than that reported with single-agent 5-FU, and responses have been seen even in patients progressing on 5-FU-containing regimens.

Another way to explain the activity of protracted treatment with tegafur, alone or with folinic acid, is for cytokinetic reasons. Obtaining responses in tumors with previous 5-FU exposure agrees with experimental data showing that prolonging the exposure of human tumor cell lines to 5-FU increases cell kill. Moreover, clinical trials have shown response rates ranging from 32 to 53% with low dose continuous infusion 5-FU in relapsed patients.[30]

The main toxicities produced by extended courses of oral tegafur alone are nausea and diarrhea, and less often mucositis and hand–foot syndrome. Myelosuppression, alopecia, and neurologic toxicity are rare.[31] We observed with our regimen an increase in the incidence of mucositis and, less pronounced, of diarrhea, but lacked of life-threatening complications. This change in toxicity profile favors the existence of a modulatory effect of low dose oral folinic acid on tegafur. The lower percentage of toxicity per administered cycle as com-

Table 4. Number of Patients With Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis	3 (12%)	2 (8%)	6 (24%)	1
Diarrhea	6 (24%)	2 (8%)	3 (12%)	—
Nausea/vomitting	5 (20%)	2 (8%)	1	—
Leukopenia	4 (16%)	—	—	—
Thrombocytopenia	1	—	—	—
Other*				

* Hand–foot syndrome, one patient; anorexia, six patients; epigastric pain, six patients.

Table 5. Percentage of Cycles With Gastrointestinal Toxicity (n = 144)

	Grade 1–2	Grade 3
Mucositis	12	10*
Diarrhea	13	3
Nausea/vomiting	6	1
Other†		

* One cycle with grade 4 mucositis.
† 5% anorexia; 5% epigastric pain.

pared with the toxicity per patient (shown in Tables 4 and 5) was due to the efficacy of symptomatic measures and dose reductions. This regimen lacks significant myelotoxicity, whereas stomatitis and diarrhea are dose-limiting toxicities, thus sharing some of the characteristics of the toxicity profile of low dose continuous infusion 5-FU and of biochemical modulation of 5-FU by folinic acid, and confirming the dose-limiting toxicities reported in Phase I trials of tegafur and folinic acid.[20–22]

Our data shows a significant activity and manageable toxicity with this all-oral regimen in patients with heavily previously treated metastatic breast cancer. This regimen can be used safely on an outpatient basis and patients may prefer the oral route to the use of intravenous chemotherapy. Randomized trials are needed to define the potential therapeutic advantage of tegafur and folinic acid over tegafur alone or 5-FU modulated by folinic acid.

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