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Oral Tegafur in the Treatment of Metastatic Breast Cancer: A Phase II Study

Mikael J. Kajanti, Seppo O. Pyrhönen and Abdel G. Maiche

Between February 1985 and October 1989, 26 patients previously treated for metastatic breast cancer received oral tegafur, at a median daily dose of 1200 mg. Of these, 21 were evaluable for response. The overall response rate was 29%; six (two in lungs, two in skin and two in lymph nodes) of 44 evaluable lesions (14%) responded to therapy. Haematological toxicity was mild, and no other dose-limiting toxicity was seen. The data indicate some activity in heavily pretreated metastatic breast cancer even after previous 5-FU therapy.
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INTRODUCTION

THE FLUOROPYRIMIDINES are one of the most useful groups of antineoplastic agents in clinical oncology with demonstrated activity against different tumours [1]. Tegafur (TG), a tetrahydro-2-furanyl derivate of 5-fluorouracil (5-FU), has shown in clinical studies antineoplastic activity comparable to that of 5-FU against several tumours, including breast cancer [2]. It acts as a depot form of 5-FU and compared to 5-FU produces little myelosuppression [1]. After intravenous infusion of TG the circulating concentrations of 5-FU are low (less than 0.1 mg/ml), suggesting that conversion to 5-FU may occur predominantly in tumour cells and the liver and that the circulating level of 5-FU may not adequately reflect the extent of this conversion [3]. High dose (2–5 g/m^2) infusion of TG is, however, often associated with severe gastrointestinal and neurological toxicity, which makes the drug unsuitable for repeated intravenous use [2]. Oral TG at a daily dose of 1000–1500 mg/m^2 causes only mild or moderate neurological and gastrointestinal toxicity in about 10–20% of patients, indicating that the oral route is more suitable for clinical use than intravenous infusion [4]. We, therefore, conducted a phase II study with oral TG in a heavily pretreated group of patients with metastatic breast cancer.

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PATIENTS AND METHODS

The eligibility criteria for the present study were histologically confirmed metastatic breast cancer, measurable lesions in one or two dimensions, age <75 years, performance status (Karnofsky index) ≥60, life expectancy >6 weeks, white blood cell count >2.0 × 10^9/l, platelets >120 × 10^9/l, and haemoglobin >100 g/l, serum creatinine <130 μmol, and serum glutamic-oxalacetic transaminase <3 × upper limit of the normal range. At least one systemic treatment, either endocrine treatment or chemotherapy, had been applied, and the disease was in a progressive

phase at admission to the study. Before admission, oral informed consent was obtained.

Patient characteristics are presented in Table 1. The median duration of disease before the start of TG was 6.3 years (range 0.8–14). All 21 evaluable patients had previously received chemotherapy and/or hormonal treatments (tamoxifen, nandrolone decanoate, medroxyprogesterone acetate and danazol) for relapsing disease (Table 2). The most commonly previously used cytostatic drugs were FAC (5-fluorouracil–doxorubicin–cyclophosphamide, 11 patients) and low-dose weekly doxorubicin (16 patients). The number of different previous systemic treatments varied from one to seven, median four. Only 1 patient had been pretreated with hormonal therapy alone.

Before treatment, physical examination, clinical laboratory tests (including carcinoembryonic antigen), and measurement of the reference lesion(s) were carried out. Routine staging procedures included computerised tomography scan or sonogram of the upper abdomen, chest X-ray and bone scan. Laboratory tests were repeated bimonthly. Adverse effects were routinely recorded on each assessment day; lesion measurements were performed at intervals of 6 weeks.

On an outpatient basis, TG was administered in daily oral doses for 14 days, which was repeated after a 14-day rest interval or when recovery from toxicity was obtained. The daily dose was 800–1000 mg/m^2, divided normally into three equal doses. The treatment was continued until progression, or discontinued at appearance of any intolerable side-effects. No other treatment (e.g. palliative radiotherapy) was given simultaneously to the patients. Patients were considered evaluable after completion of at least two courses of oral TG. Standard criteria were used for response and toxicity [5].

RESULTS

Between February 1985 and October 1989, 26 consecutive patients were entered into the study; 4 patients were not evaluable because they received only one cycle of TG (early progress of disease), and 1 patient concomitantly received intravenous chemotherapy. None of the patients refused to continue therapy. Thus, 21 patients were evaluable for response and side-effects of the treatment. A total of 112 cycles of TG were administered (median five, range two to 19) with a median daily dose of 1200 mg (range 1000–1600 mg) (Table 3).

6 of the 21 patients responded; thus, the overall response rate was 29% of evaluable patients. Response to therapy is presented in Table 4. 1 of the 17 patients with lung metastasis achieved

Table 1. Patients' characteristics

Patients	
Eligible	26
Evaluable	21
Age	
Median	64
Range	37–74
Karnofsky index	
70	13
60	8
Sites of evaluable lesions	
Lung	17 (39%)
Bone	10 (23%)
Liver	5 (11%)
Skin	9 (20%)
Lymph nodes	3 (7%)

Table 2. Previous chemo- and endocrine therapy and its outcome

	No. of patients
LDWD	2
LDWD+1	3
LDWD+AOS	1
LDWD+FAC + 3	6
LDWD+3	1
LDWD+EV+CMF+2	1
LDWD+FAC+CMF+EV+2	1
LDWD+AOS+Mtx-5-FU+4	1
FAC+CMF+E+4	1
FAC+1	2
FAC+CMF+2	1
3	1

	No.	Responses
LDWD	16	CR 3, PR 4, SD 4, PD 5
FAC	11	CR 2, PR 3, SD 3, PD 3
EV	2	SD 1, PD 1
CMF	4	CR 1, PR 1 SD 0, PD 2
AOS	2	PR 1, SD 0, PD 1
E	1	PD 1
T	18	PR 5, SD 7, PD 6
N	15	PR 3, SD 6, PD 6
MPA	10	PR 3, SD 4, PD 4
D	2	SD 1, PD 1

LDWD = Low-dose weekly doxorubicin; FAC = 5-fluorouracil+doxorubicin+cyclophosphamide; EV = epidoxorubicin+vinblastine; CMF = cyclophosphamide+methotrexate+5-fluorouracil; AOS = doxorubicin+vincristine+ cyclophosphamide. E = Epidoxorubicin; 1 = tamoxifen (T); 2 = T+nandrolone decanoate (N); 3 = T+N+medroxyprogesterone acetate (MPA); 4 = T+N+MPA+danazol (D).

Table 3. Treatment given and toxicity

No. of patients	21
Total courses	112
Median (range) courses per patient	5 (2–19)
Median (range) cumulative dose of tegafur (mg/m^2)	88.9 (33.6–723.7)
Median (range) maximum dose-cycle of tegafur (mg/m^2)	53.00 (21.82–150.33)
Haematological toxicity (lowest per patient)	
WBC (cells/μl)	
Nadir: median (range)	4.6 (1.5–8.8)
<3000/gml (all courses)	41/112 (37%)
Platelets (cells/μl)	
Nadir: median (range)	199.000 (86.000–338.000)
<100.000 (all courses)	27/112 (24%)
Gastrointestinal toxicity	
Nausea/vomiting	38% (grade 1–2)
Diarrhoea	19% (grade 1–2)
Neurological toxicity	
Dizziness/lethargy	19% (grade 1–2)

Table 4. Response by site to oral tegafur of 21 evaluable patients

Sites of lesions	*n*	CR	PR	CR+PR(%)	SD	PD
Lung	17	1	1	(6)	4	11
Bone	10	—	—	(—)	1	9
Liver	5	—	—	(—)	1	4
Skin	9	1	1	(22)	4	3
Lymph nodes	3	1	1	(66)	1	—
Total	44	3	3	(16)	11	27

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

complete remission (CR) of duration 3 months, partial response (PR) of 8 months, and 4 patients showed stable disease (SD), durations of 3, 6, 8 and 10 months. 1 patient with bone metastasis showed SD for 4 months and 1 patient with metastasis in the liver showed SD of duration 4 months. 1 of the 9 patients with skin metastasis achieved CR of duration 10 months, 1 PR of 6 months, and 4 patients showed SD for 3 months. 1 patient with metastatic disease in the lymph nodes experienced CR for 4 months, 1 patient PR for 4 months, and 1 SD for 3 months. Thus, a total of 3/44 (7%) CR of median duration 8 months and 3/44 (7%) PR of median duration 6 months in evaluable lesions was registered.

1 patient with lung metastases achieving CR from TG had previously received FAC, resulting in CR, low-dose weekly doxorubicin (LDWD), resulting in PR, and combined epidoxorubicin + tamoxifen (PR); the other responding patient with lung metastases had received LDWD (PR). 1 patient with skin metastases receiving CR for TG was previously treated with FAC (PR), LDWD (progressive disease, PD) and tamoxifen (PR), plus nandrolone decanoate (SD), and medroxyprogesterone acetate (PD), whereas the other patient with PR for TG was pretreated with LDWD (PR); 1 patient with metastatic disease in lymph nodes receiving CR for TG was previously treated with tamoxifen (PR), nandrolone decanoate (SD), and medroxyprogesterone acetate (PD); the other one receiving PR for TG was pretreated with FAC (PR), LDWD (PD), and tamoxifen (SD). Thus, a total of 3 of the 6 responders had previously received FAC. 6 patients (29%) experienced improvement, 6 stabilised, and 9 (42%) showed lower performance status during the treatment.

Haematological side-effects included grade 1–2 leukopenia in 5 (24%) patients and grade 1–2 thrombocytopenia in 2 (10%) (Table 3). Mild (grade 1–2) anaemia occurred in 1 (5%) patient. No other haematological side-effects were reported. Non-haematological toxicities were mild to moderate: grade 1–2 nausea/vomiting in 8 patients, grade 1–2 diarrhoea in 4 patients and grade 1–2 neurological toxicity in 4 patients, mainly in the form of dizziness and lethargy. No renal or cardiac toxicities were seen. In none of the patients did treatment have to be discontinued because of side-effects.

DISCUSSION

The primary goal in the treatment of patients with metastatic breast cancer is to achieve maximal palliation of the symptoms with minimal toxicity and with the longest possible time to progression. Several drugs have been tested in phase II trials over the last decades in moderately or heavily pretreated patients. One might argue that these were not given a fair chance to demonstrate activity, having been applied to patients who had developed clinical resistance to prior therapy with multiple agents and normally with a median duration of survival of only a few months.

The response rates achieved with cytostatics given as second line therapy in advanced breast cancer have varied between 0 and 40% [6]. Investigational agents have resulted response rates in up to 29% (dibromodulcitol) when reports are included with at least 15 or more evaluable patients [7]. After the use of one or more chemotherapy regimens the response rates of the combination chemotherapy regimens for the salvage treatment have varied from 3% (5-Fudr+cytarabine) [8] up to 73% (doxorubicin + mitomycin + vincristine) [9]. Despite the widespread use of the combination regimens, none of them can be considered to be sufficiently effective as to constitute standard therapy. Comparing a combination regimen (VAC, vincristine + doxorubicin + cyclophosphamide) with a single agent (doxorubicin), no appreciable difference was observed in survival between the two approaches [10].

Pooled data on a phase II study of TG given orally at a daily dose of 300–600 mg to 438 evaluable patients revealed a response in carcinoma of the stomach (27.7%), pancreas (25.0%), gallbladder and bile duct (25.0%), liver (19.2%), colon and rectum (25.0%), breast (32.0%), and lung (7.0%) [11]. The main gastrointestinal toxicity resulted in anorexia (24.3%), nausea and vomiting (12.5%), and diarrhoea (11.8%), whereas haematological toxicity was mild [11]. When the response rates with intravenous and with oral TG were compared in patients with advanced colorectal and breast cancer, almost identical figures (25 vs. 29% and 44 vs. 43%) resulted [12].

On the basis of our experience with oral TG in metastatic breast cancer, we concluded that it is a safe cytostatic drug which can be used in outpatient care with minor toxicity. 3 (27%) out of the 11 patients previously treated with 5-FU regimen responded to oral TG, which is in agreement with previous observations [12, 13], suggesting a possible lack of cross-resistance between TG and 5-FU. In none of the patients, did treatment have to be discontinued because of side-effects. A clear advantage of oral TG treatment compared to many combination chemotherapy regimens is that the treatment is very simple in its present form and can be administered even to elderly patients without frequent laboratory monitoring. In addition, the present results demonstrate activity in heavily pretreated metastatic breast cancer even after previous 5-FU therapy.

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Prevalence of Anticipatory Nausea and Other Side-effects in Cancer Patients Receiving Chemotherapy

Robert A. Boakes, Nicholas Tarrier, Benjamin W. Barnes and Martin H.N. Tattersall

98 patients receiving chemotherapy for cancer were interviewed to determine the prevalence of anticipatory nausea and vomiting, anxiety and dietary changes. Among those who had received at least four treatments 41% reported at least mild anticipatory nausea (AN). For 24% this was a moderate to severe problem, which was significantly associated with a high level of anxiety about treatment. Prevalence at this level was independent of whether the subject was receiving treatment as an in- or an outpatient. Anticipatory vomiting (AV) was reported by only 12 patients, of whom 11 were women; this was the only effect of gender found in the sample. Independence between moderate AN and AV was also suggested by a difference in type of event triggering the effect: predominantly odours for AN and thoughts of the treatment for AV. Changes in diet after commencing chemotherapy were reported by 50% of patients who had received at least four treatments. These most commonly took the form of aversions to meat and then to coffee, and were attributed most frequently to changes in taste and then to loss of appetite.
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INTRODUCTION

NAUSEA AND vomiting are common side-effects of chemotherapy for cancer patients. They are viewed by patients as the most distressing of all such effects [1], as was confirmed in the present study. Post-treatment nausea and vomiting is produced as a direct effect of chemotherapy and can last for 48 h or more after treatment. Anticipatory nausea and vomiting (ANV) occurs outside this period and has a psychological basis in the sense that it is triggered by events that have no direct physical effect. Both post-treatment and ANV are prevalent in chemotherapy despite the development and careful use of various antiemetic drugs. Consequently a number of psychological procedures, such as relaxation training and systematic desensitisation, have been used to treat ANV [2]. These are based, at least loosely, on the assumption that its psychological basis is some form of conditioning process.

The present study was undertaken as a preliminary to a project designed to compare the efficacy of different forms of treatment for ANV. Before beginning this project data were needed on the prevalence of ANV and other side-effects in the hospital setting where the project was to be undertaken. Several previous studies have measured the prevalence of ANV and have produced widely differing estimates [2, 3]. None of these was based in Australia and it seemed possible that local conditions might produce a different rate from those obtaining in North America where the majority of other studies have been carried out.

While the main point of the study was to establish the prevalence of ANV locally, many questions in the survey were on other side-effects related to psychological approaches to treatment. Thus, one conditioning model of ANV [4] places emphasis on the role of anxiety and on the therapeutic value of acquiring skills to control anxiety. Consequently, patients were asked separately about the degree to which they had experienced ANV and about anxiety concerning chemotherapy, to determine whether responses to these items might be strongly associated. A different conditioning model [5] has emphasised its similarity to nausea-based conditioning in animals where highly selective

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