Paclitaxel and UFT Plus Oral Calcium Folinate in Pretreated Metastatic Breast Cancer

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This phase I study was designed to determine the maximum tolerated dose (MTD) and dose-limiting side effects of combination treatment with paclitaxel (Taxol) and UFT (uracil and tegafur in a 4:1 molar ratio) plus oral calcium folinate.

**Introduction**

The classic example of a cyclespecific, S-phase-dependent drug with a short half-life is 5-fluorouracil (5-FU). Conventional bolus injection may not be the most effective schedule. Recent phase II study results demonstrated high efficacy and low toxicity for a weekly schedule of 24-hour infusional 5-FU/calcium folinate,[1] as well as for continuous infusion of low-dose 5-FU in intensively pretreated patients with metastatic breast cancer.[2]

Paclitaxel (Taxol) in combination with weekly high-dose 5-FU/calcium folinate constitutes a highly active salvage regimen for patients with pretreated metastatic breast cancer.[3] UFT (uracil and tegafur in a 4:1 molar ratio) may allow administration of long-term, low-dose oral 5-FU with a similar pharmacokinetic profile as a continuous infusion,[4] but without the need for central venous catheters and portable pumps. We therefore initiated this ongoing phase I study in which UFT was administered orally for 14 days with oral calcium folinate (Orzel) in combination with paclitaxel as a 3-hour intravenous infusion every 3 weeks. The data that follow were presented at the April 1999 meeting of the American Association for Cancer Research.[5]

**Patients and Methods**

**Inclusion Criteria**

Patients in this study had to have histologically proven breast cancer and a failure to respond to previous chemotherapy for breast cancer—either adjuvant, metastatic, or both. Other inclusion criteria were progressive measurable or evaluable disease, age ≥ 18 years, World Health Organization (WHO) performance status ≤ 2, life expectancy of ≥ 3 months, and adequate renal, liver, and bone marrow function (creatinine, bilirubin ≤ 1.5 × upper limit of normal and absolute neutrophil count [ANC] ≥ 2.0 × 10⁹/L, platelet count ≥ 100 × 10⁹/L). All patients gave informed consent prior to study entry.

**Staging and Follow-Up**

Prior to treatment, all patients underwent complete medical history and physical examination, electrocardiogram, determination and measurements of study parameters by chest x-ray, bone scan, and computed tomography scan and/or ultrasound. During treatment, full hematologic blood counts, determination of liver and renal functions, and assessment of nonhematologic toxicities were performed weekly. Response to treatment was assessed prior to each cycle. The standard WHO common toxicity criteria were used to evaluate response and toxicity.

**Treatment Schedule**

After standard premedication with dexamethasone (8 mg orally 12 h and 6 h prior to each paclitaxel infusion), cimetidine (Tagamet) (400 mg intravenously), and clemastine (Tavist) (2 mg IV) 30 minutes before each paclitaxel treatment, patients received paclitaxel, diluted in 1,000 mL 0.9% saline solution as a 3-hour IV infusion on day 1. Concomitantly, UFT plus oral calcium folinate was started at day 1 and continued through day 14 in three divided daily doses. The dosage administered at each dose level is described in Table 1. Cycles were repeated on day 21. Prophylactic antiemetic treatment was given according to routine practice.
Dose Escalation
The starting UFT dose was 300 mg/day orally for 14 days (Table 1). A fixed 30-mg dose of calcium folinate was given orally concurrently with each UFT dose at all dose levels. (Dosing may be repeated after a 7-day rest period or on full recovery from any toxicity.) We performed no intrapatient dose escalation. At least three patients were treated at each dose level. If none of these patients developed a dose-limiting toxicity during the first course of treatment, the next dose level was opened. Dose-limiting toxicities were defined as

1. **hematologic toxicity:** ANC < 0.5 × 10^9/L for > 7 days, ANC < 0.1 × 10^9/L for > 3 days, any episode of febrile neutropenia, platelets < 25 × 10^9/L, bleeding, absence of recovery of absolute neutrophil count and/or platelets by day 35;

2. **nonhematologic toxicity:** any toxicity of common toxicity criteria grade ≥ 3 (excluding alopecia, nausea and vomiting, myalgia, asthenia grade 3), persistence of toxicity of common toxicity criteria grade ≥ 2 at day 35 (excluding alopecia, nausea and vomiting, myalgia, asthenia grade 2), and inability to take ≥ 75% of planned UFT dose.

If one of the first three patients developed a dose-limiting toxicity, a maximum of three additional patients were treated at this dose level. If none or only one of these three additional patients developed dose-limiting toxicity, the next dose level was opened. The maximum tolerated dose was reached if three of six patients at a given dose level developed dose-limiting toxicities during any course of treatment. The recommended dose for phase II will be one dose level below the maximum tolerated dose.

Results
To date, 20 patients with pretreated metastatic breast cancer have been entered in the trial. Median age is 52 years (range 28 to 70 years). Median performance status according to WHO criteria is 1 (range 0 to 1). All included patients have had prior chemotherapy either as adjuvant treatment, for metastatic disease, or both. Four of the 20 patients had anthracycline-refractory disease, defined as disease progression while receiving anthracycline-containing chemotherapy prior to study entry. The observed toxicity at each dose level is outlined in Table 2. All patients experienced common toxicity criteria grade 3 alopecia. No dose-limiting toxicities were seen in 14 patients treated at dose levels 1 to 3 (72 treatment cycles). In the fourth dose level, one of three patients experienced a dose-limiting toxicity as neutropenic fever. According to the protocol, an additional three patients were entered at this dose level; these patients did not experience a dose-limiting toxicity. WHO grades 1 and 2 peripheral neuropathy, arthralgia, and myalgia were common but not dose-limiting. So far, no severe stomatitis or diarrhea has been observed (Table 2). All patients had disease progression, defined according to WHO criteria, prior to study entry. Of the 20 enrolled patients, one has had a complete remission, five have had partial remissions, five minor remissions, and seven stable disease; only two patients experienced progressive disease. Responses could be observed at all dose levels (Table 3). An improvement of tumor-related symptoms (pain, weight loss) was seen in all patients with an objective tumor response as well as in patients with stable disease. There has been good compliance among the patients with the oral treatment regimen, as documented by a patient diary.

Conclusions
We have not reached the maximum tolerated dose of combination paclitaxel and UFT plus oral calcium folinate within four dose levels in this ongoing phase I study. We will continue the trial with dose level 5 (paclitaxel 175 mg/m2 day 1 and UFT 700 mg total dose days 1 to 14 plus calcium folinate 90 mg days 1 to 14). Thus far, preliminary data suggest that the combination of paclitaxel and UFT plus oral calcium folinate is a convenient and effective regimen for patients with pretreated metastatic breast cancer.

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