**UFT/Leucovorin Combined With Paclitaxel for Anthracycline-Pretreated Advanced Breast Cancer**

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Taxanes are the most active drugs in the treatment of metastatic breast and ovarian cancer. Weekly therapy with paclitaxel produces notable activity, with remarkably low toxicity.

**Introduction**

Metastatic cancer is incurable. Thus, quality of life is a critical treatment issue. High efficacy, few side effects, and an outpatient setting are important criteria for patients receiving second- or third-line therapy. Currently, paclitaxel (Taxol) is the most active drug in the treatment of metastatic breast and ovarian cancer. Single-agent response rates of up to 56%,[1] or as high as 80% when used in combination with an anthracycline, have been reported.[2,3]

In recent trials, paclitaxel was administered via 24- or 3-hour intravenous (IV) infusions. Since premedication with diphenhydramine, cimetidine (Tagamet), and corticosteroids (most often dexamethasone) has been introduced into clinical practice, the frequency of hypersensitivity reactions with 3-hour paclitaxel infusions has been greatly reduced. One-hour paclitaxel infusions have been investigated primarily for the convenience of outpatient treatment. Hainsworth et al showed that 1-hour paclitaxel is safe and has substantial activity in different tumor types.[4] Several clinical trials have examined weekly administration of paclitaxel, [5-9] which is predominantly cytotoxic for dividing cells.[10] Based on the results of these trials, we can conclude that a high-dose intensity is possible with weekly paclitaxel administration. Hematologic and nonhematologic toxicities are mild and objective response rates are relatively high (30% to 48%). However, paclitaxel administered at doses above 100 mg/m²/wk may result in treatment-limiting neurotoxicity.

The development of new combination drug regimens has become an important area of clinical research in the care of patients who fail to respond during or after first-line treatment. Regimens that are based on anthracycline and alkylating agents are routinely used as first-line chemotherapy in metastatic breast cancer. Klaassen et al demonstrated high activity with combination paclitaxel/high-dose 5-FU in anthracycline-pretreated breast cancer patients. Additionally, recent studies have reported response rates of 54% to 69% for the combination of leucovorin/5-FU/paclitaxel.[11,12]

UFT (uracil and tegafur) plus oral leucovorin (a combination being developed under the trade name Orzel) is an orally available agent that provides activity comparable to 5-FU and has a favorable side-effect profile.

**Study Design**

This trial is an open-label, single-center, phase I study to investigate the combination of paclitaxel (administered in a weekly 1-hour infusion) with UFT plus leucovorin in patients with anthracycline-resistant metastatic breast cancer. The dose-limiting toxicity, the maximum tolerated dose, and the recommended dose for phase II testing will be determined.

**Eligibility**

**Inclusion Criteria**

Patients with metastatic breast cancer who have recurrent or progressive disease following therapy with anthracyclines, or patients who are unable to be treated with anthracyclines due to decreased left-ventricular cardiac function, are eligible. Patients must have histologically or cytologically proven breast cancer, and may have received hormonal, immuno-, or localized radiation, therapy.
Additionally, patients must be aged ≥ 18 and ≤ 70 years; have Eastern Cooperative Oncology Group performance status greater than 2; have a life expectancy ≥ 12 weeks; and have adequate hematologic, renal, and hepatic functions.

**Exclusion Criteria**

Exclusion criteria include prior treatment with paclitaxel, significant history of cardiac disease, evidence of peripheral neuropathy greater than Common Toxicity Criteria grade 2, and symptomatic brain metastases.

**Dose Administration**

Paclitaxel 80 mg/m²/wk is administered intravenously over 1 hour for 6 weeks. Premedication consists of dexamethasone 4 mg IV, clemastine (Tavist) 2 mg IV, and ranitidine (Zantac) 50 mg IV 30 minutes prior to paclitaxel.

UFT plus leucovorin is administered at a starting dose of 200 mg UFT (absolute dose, escalated stepwise to 700-mg absolute dose in subsequent dose levels), together with 90 mg leucovorin on days 1 to 42, followed by a 2-week period without treatment (Table 1 and Figure 1). The total dose for this combination is divided into three doses, administered orally every 8 hours. Depending on tumor response following cycle 1, treatment continues for a maximum of two cycles.

**Dose-Limiting Toxicities**

The following hematologic parameters will be considered dose-limiting toxicities (DLT): absolute neutrophil count (ANC) < 0.5 x 10⁹/L for > 7 days; ANC < 0.1 x 10⁹/L for > 3 days; any episode of febrile neutropenia (temperature >38.2°C, granulocytes < 0.5 x 10⁹/L, requiring IV antibiotics; platelets < 25 x 10⁹/L; and bleeding requiring platelet transfusion. Additional parameters for dose-limiting toxicities are any nonhematologic toxicity Common Toxicity Criteria grade ≥ 3 (excluding alopecia, inadequately treated grade 3 vomiting, and grade 3 severe asthenia).

A minimum of three patients will be treated at any given dose level. Every patient treated at a given dose level must complete course 1. Full evaluation of toxicity at that dose level must correspond to dose-limiting toxicity and maximum tolerated dose criteria before the next dose level is implemented. If one of the first three patients at a given dose level experiences dose-limiting toxicity, up to three more patients will be treated at this level.

**Results**

**Patient Characteristics**

This phase I trial opened in September 1998. As of June 1999, 15 patients have entered the study; 11 are evaluable for toxicity. The median age is 55 years. Baseline patient characteristics are noted in Table 2.

**Toxicity by Dose Increments**

Of the 11 evaluable patients, four were treated at dose level 1 (paclitaxel 80 mg/m², UFT 200-mg absolute dose) and seven were treated at dose level 2 (paclitaxel 80 mg/m², UFT 300-mg absolute dose) without any problems. Two patients at dose level 2 received only one treatment cycle due to disease progression. Four patients are still in the study at dose level 3 (paclitaxel 80 mg/m², UFT 400-mg absolute dose). It is too early to provide results from this dose level.

**Hematologic and Nonhematologic Toxicities**

No severe hematologic or nonhematologic toxicities were observed in dose levels 1 and 2. No cases of febrile neutropenia were observed (Table 3).

**Conclusions**

The first patients in dose levels 1 and 2 tolerated the treatment without any adverse effects. No severe hematologic and nonhematologic toxicities were observed. At dose level 3 (paclitaxel 80 mg/m², UFT 400-mg absolute dose), four patients are still in study. Although it is too early to provide results from this dose level, results from recent studies of monotherapy with weekly paclitaxel or UFT plus leucovorin in metastatic breast cancer suggest that the combination may produce higher activity with a low incidence of side effects in anthracycline-pretreated patients. The final results from this study may offer a second- or third-line therapy for metastatic disease that has high efficacy, few side effects, and takes place in an outpatient setting.
References:


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