UFT Plus Oral Calcium Folinate/Vinorelbine for Advanced Breast Cancer

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By Pierre Fumoleau, MD [2], Régine Déporte-Fety, PhD [3], Pierre Kerbrat, MD [4], and Brigitte Laguerre, MD [5]

This phase I study was undertaken to define the maximum tolerated dose, dose-limiting toxicity, and recommended dosage of UFT (uracil and tegafur) plus oral calcium folinate (Orzel) and vinorelbine (Navelbine) in

Introduction

Despite adequate primary treatment at the time of diagnosis (surgery with or without adjuvant radiation or chemotherapy), 25% to 30% of patients without histologic signs of axillary node involvement, and up to 80% of node-positive patients relapse and subsequently die of metastatic breast cancer.[1,2] Although adjuvant treatment may delay recurrence and improve survival in a small number of patients,[3] therapy for metastatic disease remains palliative in intent. Some lengthening of survival duration, however, has been demonstrated with combination regimens in selected patients with advanced disease.[4]

Metastatic breast cancer is moderately sensitive to anticancer chemotherapy, and mean objective response rates of 20% to 50% have been achieved with single-agent treatment with anthracyclines, alkylating agents, 5-fluoro-uracil (5-FU), methotrexate, vinca alkaloids, and, more recently, taxanes.[5-7] Regimens that combine anthracyclines and taxanes are very effective and provide the highest overall response rates (up to 90%) as front-line therapy for advanced disease.[8,9] In the future, these combinations will potentially be used in adjuvant and/or neoadjuvant situations.[10] There remains, nonetheless, the need for new, non-anthracycline, non-taxane-based combination regimens that are effective in patients with metastatic breast cancer.

Background

Vinorelbine (Navelbine) is a semisynthetic derivative of vinblastine. Both drugs exert their antineoplastic action by preventing tubulin polymerization and arresting mitosis at metaphase.[11,12] Vinorelbine was specifically designed to bind with mitotic tubulin,[13] and in early studies, it provided activity similar to that of the anthracyclines.[6] As a result of vinorelbine’s structural modification, it has a reduced effect on axonal microtubules compared with other vinca alkaloids, and as a result, may be less neurotoxic.[14]

In phase II studies, single-agent intravenous vinorelbine 30 mg/m² weekly as first-line chemotherapy for metastatic disease produced response rates of 41% to 60% in patients with advanced breast cancer.[15-20] In studies of second-line therapy, vinorelbine yielded an overall response rate of 17% to 36% in patients with previously treated breast cancer.[19,21-23] Although most phase II studies have been designed to administer single-agent vinorelbine at a dose of 30 mg/m² weekly,[12,18] the mean dose intensity achieved has only been 65% to 70% of the planned dose (20-23 mg/m²/week) due to the dose delays for neutropenia and/or its complications.[24]

UFT is composed of uracil and tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) in a molar ratio of 4:1. In one double-blind, randomized study of this agent,[25] 56 evaluable patients with advanced breast cancer received either UFT at a dose of 400 mg/day or tegafur at a dose of 800 mg/day. Although no statistically significant difference in response rate was detected between the two arms (39% in the UFT arm and 21% in the tegafur arm), there was a trend favoring UFT for median time to progression: 37 weeks in the UFT arm vs 28 weeks in the tegafur arm (P = .09).

In a phase II study of first-line treatment of metastatic breast cancer, Daniels et al evaluated the combination of UFT 10 mg/kg/day and calcium folinate 90 mg/day (days 7 to 21) with carboplatin
The response rate was 48% among 23 evaluable patients. Grade 3 neutropenia occurred in five patients and diarrhea in three. Recently, Villalon et al.[27] performed a randomized phase II study to compare the activity of UFT at a dose of 350 mg/m²/day from day 1 to day 14 vs 5-FU 500 mg/m²/day on day 1 and day 8, both in combination with doxorubicin (Adriamycin) 50 mg/m² and cyclophosphamide (Cytoxan) 500 mg/m² on day 1. Among 62 evaluable patients, there was no statistical difference in overall response rate (UFT = 48.4%; 5-FU = 35.5%), and median response duration was 16 weeks in both arms. Toxicity was low with both regimens.[27]

Vinorelbine has been combined in a continuous infusion with 5-FU or with 5-FU plus calcium folinate. In first-line treatment of metastatic breast cancer, vinorelbine (30 mg/m² on days 1 and 5) in combination with 5-FU (750 mg/m² in a continuous infusion from days 1 to 5) produced a 61.6% response rate in 63 evaluable patients.[28] Using the same schedule, Vogel et al reported a 40% overall response rate among 47 evaluable patients with metastatic breast cancer.[29] A second-line therapy of vinorelbine (30 mg/m² on day 1) plus 5-FU (750 mg/m²/day in a continuous infusion from days 1 to 3) yielded an overall response rate of 31% in 16 patients.[30] In all of these studies, however, toxicity was greater than that noted with single-agent vinorelbine, and the 30 to 25 mg/m²/week starting doses were not maintained throughout treatment. In a phase II pilot study by Mardiak et al.[31] 15 previously untreated patients receiving vinorelbine (20 mg/m² on days 1 and 8) in combination with 5-FU (500 mg/m² on days 1 and 8) and calcium folinate (200 mg/m² on days 1 and 8) for metastatic breast cancer experienced a 73% (11 of 15 patients) overall response rate.[31]

Thus, given the need for new, effective, non-anthracycline, non-taxane-based chemotherapies for metastatic breast cancer, and based on the significant single-agent clinical activities of vinorelbine and UFT plus oral calcium folinate, a nonrandomized, phase I, dose-escalating study of their combination was planned. The primary objectives of the study were to determine the maximum tolerated dose, dose-limiting toxicity, and recommended doses of UFT and vinorelbine for the treatment of metastatic breast cancer in patients who had previously received one chemotherapy regimen. In addition, the pharmacokinetics of UFT and vinorelbine when used in combination were also evaluated.

**Patients and Eligibility Criteria**

Women aged ≥18 years with metastatic breast cancer were accrued into this phase I, dose-finding study conducted at two centers. The trial received ethical committee approval and all patients provided written, informed consent. Inclusion was based on histologically proven breast cancer with evidence of measurable and/or evaluable metastatic disease. Patients must have received one prior chemotherapy regimen for the treatment of metastatic breast carcinoma. Prior neoadjuvant and/or adjuvant chemotherapy were permitted. Cytotoxic or radiation therapy must have been terminated for at least 4 weeks.

Other eligibility criteria were World Health Organization (WHO) performance status ≤2, absolute neutrophil count (ANC) ≥2 × 10⁹/L, platelet count ≥100×10⁹/L, serum creatinine ≤1.5 × upper limit of normal (ULN), aspartate transaminase and alanine transaminase ≤2 × ULN, and bilirubin ≤1.25 × ULN. Patients previously treated with a vinca alkaloid or continuous infusion 5-FU, either in the adjuvant or metastatic setting, were ineligible.

**Treatment Dosages**

Starting doses for the combination regimen were lower than those recommended for the respective single agents, but were still expected to yield acceptable levels of efficacy, as described earlier. Thus, the first dosage level was vinorelbine 15 mg/m² on days 1, 8, and 15 and UFT 300 mg/day, plus a fixed calcium folinate dose of 90 mg/day, both in three divided daily doses on days 1 through 21. Vinorelbine was injected on days 8 and 15, provided the ANC was greater than 1.5 × 10⁹/L and/or platelet count was greater than 75 × 10⁹/L on those days. Treatment cycles were repeated every 28 days, provided blood cell counts had recovered and nonhematologic toxicity had resolved to grade ≤1. Treatment could be delayed as long as 2 weeks if ANC remained < 1.5 ×10⁹/L and/or platelets < 75 ×10⁹/L. The prophylactic use of recombinant human granulocyte colony-stimulating factor was not routinely permitted.

Doses of vinorelbine and UFT were escalated in each successive cohort of new patients (Table 1). Three patients were treated at each dose level, with a 2-week interval between entry of the first patient and the next two patients. Intraindividual dose escalation was not permitted. If one of three patients at a dose level developed a dose-limiting toxicity, three more patients were entered at the same dose level. Patients who experienced dose-limiting toxicity were removed from treatment until the toxicity had resolved to grade ≤1, and were then restarted for the subsequent cycle at the next lower dose level.
Doses that had been reduced for toxicity in individual patients could not be re-escalated.

**Dose-Limiting Toxicity and Maximum Tolerated Dose**

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Dose-limiting toxicity was defined during the first cycle as: 1) any of the following hematologic toxicities: grade 4 neutropenia lasting > 7 days, febrile neutropenia (defined as grade 4 neutropenia plus fever grade \( \geq 2 \)), or grade 4 thrombocytopenia; 2) grade 3/4 nausea, vomiting, or diarrhea despite appropriate treatment; 3) any other grade 3/4 nonhematologic toxicity (with the exception of alopecia and fatigue); 4) inability of patients to take full UFT doses for \( \geq 3 \) of 21 days; 5) delay in start of second cycle (day > 29); and 6) inability to take one of the three vinorelbine doses because of toxicity.

The maximum tolerated dose was defined as the dose at which two or more of three, or three or more of six patients developed a dose-limiting toxicity.

**Treatment Administration Guidelines**

UFT was administered orally in three divided daily doses. Vinorelbine was administered as a 5-minute intravenous infusion.

- The sequence for cycle 1, days 1, 8, and 15, was UFT first dose 7:00 am; vinorelbine 6 hours after (1:00 pm); UFT second dose 3:00 pm; and UFT third dose 11:00 pm.

- The sequence for cycle 2, days 1, 8, and 15, was vinorelbine first dose 7:00 am; UFT first dose 7:10 am; UFT second dose 3:10 pm; and UFT third dose 11:10 pm.

- For the subsequent cycles, the sequence for days 1, 8, and 15 was UFT first dose 7:00 am; vinorelbine at the investigator’s discretion after the first dose of UFT; UFT second dose 3:00 pm; and UFT third dose 11:00 pm.

Treatment was continued unless there was evidence of disease progression, unacceptable toxicity, or patient refusal.

**Patient Evaluation**

Pretreatment evaluations included medical history; physical examination and vital signs; WHO performance status; left ventricular ejection fraction; tumor measurements (chest x-ray, abdominal computed tomography [CT] scan, or ultrasound and CT scans of all measurable and/or evaluable lesions); complete blood cell count (white blood cells, platelets, hemoglobin); blood biochemistry and urinalysis; liver function tests; and electrocardiogram. During treatment, hematologic measurements were performed twice weekly. To assess response, tumor measurements were repeated every two cycles, or every cycle, if clinically indicated.

Patients who had received at least two cycles of therapy were evaluable for response to treatment according to standard WHO criteria[32] unless disease progression was noted prior to cycle 2, in which case, treatment was considered to have failed.

**Pharmacokinetic Analysis**

The pharmacokinetics of UFT and vinorelbine were evaluated during the first treatment cycle. For UFT, blood samples were collected before the first dose on day 1, then 30 minutes and 1, 1.5, 2, 2.5, 4, and 6 hours after the first dose. In addition, samples were collected on days 8, 15, and 21 as follows: before the first daily dose, then 30 minutes and 1, 1.5, 2, and 6 hours after this dose. For vinorelbine, blood samples were collected on day 1 immediately before the 5-minute infusion that was administered 6 hours after the first dose of UFT, then 5, 10, 20, 35 minutes, 1:35, 3:35, 6:35, 10:35, and 18 hours after the start of infusion.

The pharmacokinetics of UFT were also evaluated during the second treatment cycle. Vinorelbine was infused first, 10 minutes before UFT. Blood samples were collected at day 1 before the first dose, and 30 minutes and 1, 1.5, 2, 2.5, 4, and 6 hours after this first dose. In addition, samples were collected on days 8, 15, and 21 before the first daily dose, then 30 minutes and 1, 1.5, 2, and 6 hours after this dose.

For both drugs, the analysis focused on the area under the plasma concentration-time curve (AUC) and total plasma clearance. The half-lives (\( t_{1/2,\alpha} \), \( t_{1/2,\beta} \), \( t_{1/2,\gamma} \)) and volume of distribution at steady state (\( V_{ss} \)) were also estimated.

**Preliminary Results**

**Patient Characteristics and Treatment Administration**
As of September 1, 1998, nine patients (age 48 to 70 years) have been treated with UFT plus vinorelbine as second-line cytotoxic therapy for metastatic breast cancer, at dose levels 1 and 2 (Table 2). Five patients had a WHO performance status of 0, and three had a WHO performance status of 1. Five of nine patients had liver metastases. Because of one patient with dose-limiting toxicity, six patients were treated at dose level 1. Level 2, with three patients enrolled and one patient with dose-limiting toxicity, is currently being studied. A total of 18 cycles of UFT/vinorelbine have been administered. At level 1, because of progressive disease, five patients have received only two cycles; although the last patient has received six cycles.

**Hematologic Toxicity**

Thus far, no grade 3/4 episodes of hematologic toxicity have been observed. One patient at each dose level, however, was unable to take one of the three vinorelbine doses because of grade 2 neutropenia at day 15 (dose-limiting toxicity).

**Nonhematologic Toxicity**

No grade 3/4 nonhematologic toxicities have been observed. Table 3 illustrates the overall incidence of grade 1/2 nonhematologic toxicities, including nausea/vomiting, diarrhea, constipation, hand/foot syndrome, fatigue, and stomatitis.

**Pharmacokinetics**

The pharmacokinetics of UFT and vinorelbine were evaluated in the six patients enrolled at level 1. For the AUC$_{0-6h}$ of 5-FU, uracil, and tegafur, the results are shown in Table 4. For the patient who developed a dose-limiting toxicity at day 15 (inability to give the vinorelbine dose because of grade 2 neutropenia), the AUC$_{0-6h}$ of 5-FU and uracil were significantly higher (P < .01) than noted for the other patients. The vinorelbine pharmacokinetic values are reported in Table 5 for these five patients.

**Efficacy**

The six patients at level 1 were evaluable for antitumor response. One had a partial response in liver metastasis. The remaining five patients experienced disease progression after two cycles.

**Conclusion**

We report the very preliminary results of an ongoing study that is currently enrolling patients at dose level 2. Two patients with dose-limiting toxicity have been observed: one patient at each dose level was unable to receive one of the three vinorelbine doses because of grade 2 neutropenia at day 15. The pharmacokinetic study involving the six patients at level 1 has indicated a significant increase at day 15 of AUC$_{0-6h}$ of 5-FU and uracil for the patient with dose-limiting toxicity.

**References:**


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