This phase I study was undertaken to define the maximum tolerated dose, the dose-limiting toxicity, and the recommended dose of UFT plus leucovorin in combination treatment of patients with metastatic breast cancer previously treated with one chemotherapy regimen. The pharmacokinetics of UFT and vinorelbine were also evaluated.

**Introduction**

Despite adequate primary treatment at the time of diagnosis (surgery with or without adjuvant radiation or chemotherapy), 25% to 30% of patients with no histologic signs of axillary node involvement and up to 80% of node-positive patients relapse and 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 has been demonstrated with combination regimens in selected patients with advanced disease.[4]

Metastatic breast cancer is moderately sensitive to anticancer chemotherapy. Mean objective response rates of 20% to 50% have been achieved by treatment with single-agent anthracyclines, alkylating agents, fluorouracil (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 may be used in the adjuvant and/or neoadjuvant settings.[10] There remains, nonetheless, the need for new, nonanthracycline, 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 in breast cancer, it provided activity similar to the anthracyclines.[6] As a result of its structural modification, vinorelbine has a reduced effect on axonal microtubules compared with other vinca alkaloids, and consequently may be less neurotoxic.[14] In phase II studies, single-agent, intravenous (IV) 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 overall response rates of 17% to 36% in patients with previously treated breast cancer.[19,21-23] Although most phase II studies were designed to administer single-agent vinorelbine at a dose of 30 mg/m²/wk,[12,18] the mean dose intensity achieved was only 65% to 70% of the planned dose (20 to 23 mg/m²/wk) due to dose delays for neutropenia and/or its complications.[24] In one double-blind, randomized study,[25] 56 evaluable patients with advanced breast cancer received either UFT (uracil and tegafur) at 400 mg/d or tegafur at 800 mg/d. Although there was no statistical significance in response rate 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/d and leucovorin 90 mg/d (days 7 to 21) with carboplatin (Paraplatin) 100 mg/m²/d (days 1 to 3) and etoposide (VePesid) 100 mg/m²/d (days 1 to 3). The response rate was 48% among 23 evaluable patients. Grade 3 neutropenia occurred in five patients and diarrhea in...
three.[26] Recently, Villalon et al performed a randomized phase II study of UFT at 350 mg/m²/d (days 1 to 14) vs 5-FU at 500 mg/m²/d (days 1 and 8), both in combination with doxorubicin (Adriamycin) at 50 mg/m² and cyclophosphamide (Cytoxan, Neosar) 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%); median response duration was 16 weeks in both arms. Toxicity was low with both regimens.[27]

Vinorelbine has been combined with 5-FU as a continuous infusion or with 5-FU plus leucovorin. In first-line treatment of metastatic breast cancer, vinorelbine (30 mg/m² on days 1 and 5) combined 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] Second-line therapy of vinorelbine (30 mg/m² on day 1) plus 5-FU (750 mg/m²/d in a continuous infusion on 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/wk starting doses were not maintained throughout treatment. In a phase II pilot study by Mardiak et al, 15 previously untreated patients with metastatic breast cancer receiving vinorelbine at 20 mg/m² (days 1 and 8) in combination with 5-FU at 500 mg/m² (days 1 and 8) and leucovorin at 200 mg/m² (days 1 and 8) experienced a 73% (11 of 15 patients) overall response rate.[31]

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

**Patients and Eligibility Criteria**

Women aged ≥ 18 years with metastatic breast cancer were accrued into this phase I, dose-finding study, conducted at three 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 was 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, aspartate transaminase and alanine transaminase ≤ 2 × upper limit of normal, and bilirubin ≤ 1.25 × upper limit of normal. Patients previously treated with a vinca alkaloid or a continuous infusion of 5-FU, either in the adjuvant or metastatic setting, were ineligible.

**Treatment Dosage**

Starting doses for the combination of vinorelbine and UFT plus leucovorin 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/d plus a fixed leucovorin dose of 90 mg/d, both in three divided daily doses on days 1 through 21. Vinorelbine was injected on days 8 and 15, provided ANC > 1.5 × 10⁹/L and platelets > 75 × 10⁹/L. Treatment cycles were repeated every 28 days, provided blood cell counts had recovered and any nonhematologic toxicity had resolved to grade ≤ 1. Treatment could be delayed for up to 2 weeks if ANC remained < 1.5 × 10⁹/L and/or platelet count was < 75 × 10⁹/L. The prophylactic use of a 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 the entry of the first patient and the next two patients. Intraindividual dose escalation was not permitted. If one of three patients at one 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 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...
Because of significant dose-limiting toxicities reported at dose level 2, which was considered the maximum tolerated dose, the study was amended and the dose-escalation scheme was modified (Table 2). For subsequent levels, the administration of vinorelbine on day 15 was removed.

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

Toxicity was graded according to the National Cancer Institute’s Common Toxicity Criteria. 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 ≥ 2), or grade 4 thrombocytopenia; (2) grade 3/4 nausea, vomiting, or diarrhea despite appropriate treatment; (3) any other nonhematologic toxicity grade 3/4 (with the exception of alopecia and fatigue); (4) inability of patients to take full UFT doses during ≥ 3 of 21 days; (5) delay in start of the second cycle (day > 29); and (6) inability to take one of the three vinorelbine doses for dose levels 1 and 2 or one of the two vinorelbine doses for the subsequent dose levels 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 IV infusion.

- The sequence for cycle 1, days 1, 8, and 15, was UFT first dose at 7:00 am; vinorelbine 6 hours later at 1:00 pm; UFT second dose at 3:00 pm; and UFT third dose at 11:00 pm.
- The sequence for cycle 2, days 1, 8, and 15, was vinorelbine at 7:00 am; UFT first dose at 7:10 am; UFT second dose at 3:10 pm; and UFT third dose at 11:10 pm.
- For the subsequent cycles, the sequence for days 1, 8, and 15 was UFT first dose at 7:00 am; vinorelbine at the investigator’s discretion after the first dose of UFT; UFT second dose at 3:00 pm; and UFT third dose at 11:00 pm. The third injection of vinorelbine on day 15 was given for dose levels 1 and 2 and removed for subsequent dose levels.

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

**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. Tumor measurements were repeated every two cycles, or every cycle if clinically indicated, in order to assess response. 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 the patient 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 before the 5-minute infusion, which was administered 6 hours after the first dose of UFT, then 5, 10, 20, and 35 minutes and 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 the first daily UFT dose. 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 the first dose. In addition, samples were collected on days 8, 15, and 21, before the first daily dose, then 30 minutes and 1, 1:30, 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 ($t_{1/2a}$, $t_{1/2bb}$, $t_{1/2gg}$) and volume of distribution at steady state ($V_{ss}$) were also estimated.
Preliminary Results

Patient Characteristics and Treatment Administration
As of September 1, 1999, 22 patients (aged 41 to 70 years) have been treated with UFT and vinorelbine as second-line cytotoxic treatment for metastatic breast cancer. Twelve patients had one metastatic site, 8 had two metastatic sites, and 2 had three metastatic sites. Because of one patient with dose-limiting toxicity, six patients were treated at dose level 1. Dose level 2, with six patients enrolled and three patients with dose-limiting toxicity, was considered the maximum tolerated dose. The dose-escalation scheme was subsequently modified, with the removal of the third administration of vinorelbine on day 15. Three patients have been enrolled at level 3, and three at level 4 with no dose-limiting toxicity. Level 5, with four patients enrolled and one patient with dose-limiting toxicity, is currently being studied. A total of 80 cycles of UFT/vinorelbine were administered. At levels 1 and 5, two patients received only one cycle due to toxicity. Six patients were treated for only two cycles because of early progressive disease, reported mainly at levels 1 and 2.

Toxicity
Thus far, no episodes of grade 4 hematologic toxicity have been observed. However, because of grade 2/3 neutropenia at day 15, one patient at level 1 and three patients at level 2 were unable to take one of the three vinorelbine doses; one patient at level 5 was also unable to take one of the two vinorelbine doses (dose-limiting toxicity). No grade 3/4 nonhematologic toxicities were observed during the first cycles. In addition, the incidence of grade 3/4 episodes was very low for subsequent cycles (2% nausea, 4% vomiting, 2% diarrhea, 2% fatigue). Table 4 illustrates the overall incidence of nonhematologic toxicities, including nausea and vomiting, diarrhea, constipation, hand/foot syndrome, fatigue, stomatitis, and headache.

Pharmacokinetics
The pharmacokinetics of UFT and vinorelbine were evaluated in the 12 patients enrolled at levels 1 and 2 (receiving UFT 300 mg/d) and in five patients treated at levels 3 and 4 (receiving UFT 400 mg/d). At levels 1 and 2, the mean area under the concentration-time curve (AUC₀-₆ₖ) of 5-FU was 0.68 ± 0.53 µmol/L × h, and at levels 3 and 4, 4.39 ± 3.91 µmol/L × h. Thus, the increase of the AUC₀-₆ₖ of 5-FU was more than dose-proportional. For the five patients who developed a dose-limiting toxicity at day 15 (inability to give the vinorelbine dose because of grade 2/3 neutropenia), the AUC₀-₆ₖ values of 5-FU were significantly higher (P < .01) than noted for the other patients. The removal of one administration of vinorelbine at dose levels 3 and 4 has allowed for increased UFT dosage and AUC₀-₆ₖ of 5-FU, with no dose-limiting toxicity reported for these patients. No pharmacokinetic interaction between UFT and vinorelbine was observed.

Efficacy
Eighteen patients were evaluable for antitumor response. One had a complete response obtained after three cycles and four had partial responses. Four of five responses were observed at dose level 3 and higher. Seven patients experienced stable disease and disease progressed in the remaining six patients after two cycles.

Conclusions
We reported the preliminary results of this ongoing study, that is currently enrolling patients at dose level 5. With vinorelbine administered at days 1, 8, and 15, the maximum tolerated dose was reached at level 2 (UFT 300 mg/d, days 1 through 21, vinorelbine 20 mg/m²). At levels 1 and 2, four patients with dose-limiting toxicities were reported: one patient at level 1 and three patients at level 2 were unable to receive one of the three vinorelbine doses because of grade 2/3 neutropenia at day 15. In addition, at dose level 2 one of these three patients was unable to receive full doses of UFT for > 3 of 21 days. The removal of one administration of vinorelbine at dose levels 3 and 4 has allowed for increased UFT dosage (400 mg/d on days 1 through 21) with no dose-limiting toxicity reported for six patients. Dose level 5 is currently being studied (UFT at 500 mg/d on days 1 through 21, vinorelbine at 25 mg/m² on days 1 and 8).

Twenty-two patients received UFT plus leucovorin and vinorelbine as second-line cytotoxic treatment for advanced disease. Eighteen patients were evaluable for antitumor response. One patient had a complete response obtained after three cycles, four had partial responses. The responses were mainly observed at dose levels 3 and above. Comparing dose levels 1 and 2 with levels 3 and 4, the increase of the AUC₀-₆ₖ of 5-FU was more
than dose-proportional. For the four patients who developed a dose-limiting toxicity at day 15, the $AUC_{0-6\text{ h}}$ values of 5-FU were significantly higher than noted for the other patients. The removal of one administration of vinorelbine at dose levels 3 and 4 has allowed for increased UFT dosage and $AUC_{0-6\text{ h}}$ of 5-FU, with no dose-limiting toxicity reported. No pharmacokinetic interaction between UFT and vinorelbine was observed.

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