Fluorouracil-Based Combinations in the Treatment of Metastatic Breast Cancer

By Ute Klaassen, MD [2] and Hans Jochen Wilke, MD [3]

Although combination chemotherapy regimens may prolong survival for selected patients with metastatic breast cancer, few, if any, are cured. The standard regimens used in treatment, eg, CMF (cyclophosphamide,

During the 1990s, one in nine women in the western world will be diagnosed with breast cancer in their lifetime, and more than 58,000 will die of the disease each year in Europe alone. Recent changes in the primary treatment of operable breast cancer have not altered patient prognosis. Adjuvant therapy delays systemic recurrence and improves survival for only a select fraction of these patients.

Therapy for metastatic breast cancer has not improved significantly in recent years. Although many combination chemotherapy regimens result in high response rates, complete remissions occur in fewer than 20% of patients, and median survival is generally 2 years. In women who do not respond to primary therapy for metastatic disease, complete remissions are infrequent, with overall response rates for most regimens ranging from 10% to 35%.[1] Given the dearth of active agents capable of inducing durable remissions in metastatic breast cancer, there is clearly a need for new therapeutic strategies, as well as the incorporation of new drugs into these strategies.

Results of studies have suggested that fluorouracil (5-FU) administered by continuous infusion has significant clinical activity in heavily pretreated breast cancer patients, with reported response rates of 25% to 40%.[2-4] A substantial body of experimental data indicates that the addition of pharmacologic concentrations of reduced folates to human tumor cells in vitro enhances both the duration and degree of thymidylate synthase inhibition produced by 5-FU.[10-12] Studies have shown that folinic acid (leucovorin) enhances the therapeutic activity of 5-FU, especially in colorectal carcinoma.[5-8] In order to extend this area of biochemical modulation and build on the results obtained with a monthly schedule of 5-FU/folinic acid in advanced colorectal carcinoma, several groups performed phase II trials using this combination in patients with previously treated metastatic breast cancer.[1,9] The results of these studies indicated that the combination has a significant therapeutic effect and can be administered with an acceptable level of toxicity in this palliative situation.

Moreover, several phase II trials have shown that 5-FU plus folinic acid is active in breast cancer patients pretreated with anthracycline-containing regimens.[1,13-15] In these trials, folinic acid and 5-FU were usually administered by bolus injection. However, phase II studies in colorectal cancer have suggested that weekly administration of high-dose folinic acid in combination with high-dose 5-FU given as a continuous 24-hour IV infusion induces higher overall response rates.[16] Similarly, our in vitro and clinical data indicate higher activity when this combination is given as a protracted infusion.[2-4,32]

Phase I/II Studies in Metastatic Breast Cancer

Weekly 24-Hour Infusion of 5-FU Plus Folinic Acid

Based on these results, we performed a phase I/II study of weekly high-dose 5-FU/folinic acid in patients with heavily pretreated metastatic breast cancer (ie, at least two prior treatment regimens).[17] All patients included had to have bidimensionally measurable disease. In the phase I portion of this study, folinic acid (500 mg/m² via a 2-hour IV infusion) was followed by 5-FU (2 g/m² via a 24-hour IV infusion) once weekly for 6 weeks followed by 2 weeks of rest. Our data demonstrated that folinic acid and 5-FU can safely be administered at these doses.

The response rate achieved in the 32 patients treated during the phase II portion was 41% (95% confidence interval [CI], 24% to 58%) with a median response duration of 11 months. Similar results were observed in the anthracycline-resistant subgroup of patients (resistance defined as progression...
while receiving anthracycline-containing chemotherapy).

**Paclitaxel Plus Weekly High-Dose 5-FU/Folinic Acid**

Our encouraging data using weekly high-dose 5-FU/folinic acid in the treatment of heavily pretreated breast cancer patients, and the promising antineoplastic activity of the tubulin-binding agent paclitaxel (Taxol) when given as second-line single-agent treatment in metastatic breast cancer[19-25] led us to initiate, in September 1993, a phase I/II study using paclitaxel in combination with weekly high-dose 5-FU/folinic acid.[31] Patients were treated with weekly high-dose 5-FU (24-hour) plus folinic acid (2-hour infusion prior to 5-FU) for 6 weeks; in addition, paclitaxel (3-hour infusion) was administered on days 1 and 22 after standard premedication with corticosteroids and histamine-1- and histamine-2-receptor antagonists. Each cycle comprised 6 weeks followed by 2 weeks’ rest. All patients were treated on an outpatient basis using IV port systems and portable pumps.

First, a classic phase I study was performed in 16 patients, four at each of four dose levels. These 16 patients underwent 56 treatment cycles. No dose-limiting toxicities occurred at dose levels 1 to 3. Because of the moderate toxicity at dose level 4, together with responses (partial responses) seen at all dose levels in two of the four patients, dose level 4 was selected for further evaluation during phase II of the study (Figure 1).

A total of 46 patients were evaluated further for response in phase II. All had measurable disease. Thus far, 35 patients are evaluable for response; 11 patients are at too early a stage to evaluate. Tables 1 and 2 summarize the characteristics and pretreatment patterns in the entire group of 46 patients.

The 46 patients have received 108 treatment cycles, with a median of three treatment cycles per patient (range, one to five). Alopecia (World Health Organization [WHO] grade 3) was common. The incidences of other toxicities are shown in Table 3. No serious acute hypersensitivity reactions to paclitaxel were observed.

Neutropenia was common but was mild to moderate in severity in most patients. No hospitalizations because of febrile neutropenia were necessary. The duration of grade 3 or 4 neutropenia was generally brief. No cytokines were used.

Besides alopecia, nonhematologic toxicities consisted mostly of mild to moderate myalgia, diarrhea, mucositis, nausea and vomiting, and hand-foot-syndrome (Table 3). Peripheral polyneuropathy was cumulative, was mild to moderate in severity, and occurred mostly during the third treatment cycle. Responses in the entire group of patients are summarized in Table 4. Complete remissions occurred in 3% of patients (1/35), partial remissions in 51% (18/35), stable disease in 40% (14/35), and progressive disease in 6% (2/35). Thus, the overall response rate was 54% (95% CI, 37% to 69%). Responses in the 20 patients with anthracycline-resistant disease (defined as progression while receiving anthracycline-containing chemotherapy) were analyzed separately (Table 5). In this subgroup, the response rate was 55% (11/20; 95% CI, 34% to 76%). Time to maximum response was 2 months (range, 1 to 5 months) remission duration was 8+ months (range, 2 to 11 months), and median follow-up was 6 months.

**Discussion**

The results of our studies must be analyzed in the context of all phase II studies of the treatment of anthracycline-resistant metastatic breast cancer. This situation is a negative prognostic factor for response to salvage chemotherapy. The collected phase II experience shows that, after prior exposure to anthracyclines, second- or third-line chemotherapy induces objective remission rates of 15% to 30% at best.[18]

Previous studies have shown that conventional doses of 5-FU/folinic acid achieve a 29% response in patients who have received one prior treatment regimen and a 22% cumulative response rate in patients who have received two prior treatment regimens.[1,9,13-15] In our study of weekly high-dose 24-hour 5-FU in combination with folinic acid, the results seemed to be superior to those of conventional 5-FU/folinic acid bolus therapy, as discussed previously.[17] The introduction of a new class of active drugs in breast cancer—the taxanes (paclitaxel and docetaxel [Taxotere])—offered a chance to further improve therapeutic outcome.[19-24]

In the phase I/II study described above, as well other phase I/II studies,[29] we showed that other drugs (cisplatin [Platinol], paclitaxel) can be safely added to weekly high-dose infusional 5-FU without compromising dose and dose intensity and without increasing toxicities to an intolerable degree. The latter fact is of crucial importance in view of the palliative intent of salvage chemotherapy in advanced breast cancer patients.
Furthermore, the combination of paclitaxel with weekly high dose 5-FU/folinic acid was well tolerated and can safely be administered under outpatient conditions. Despite full doses of both 5-FU and paclitaxel, only 14% and 7% of all treatment cycles were associated with WHO grade 3/4 myelotoxicity and diarrhea, respectively. Most side effects were mild and of short duration. Of note is the 54% response rate induced by high-dose 5-FU/folinic acid/paclitaxel in patients who had received prior chemotherapy, especially those who had anthracycline-refractory disease. The results of our study thus far are noteworthy when compared with those of other combinations in the second-line treatment of advanced breast cancer.

Conclusions and Future Directions

Fluorouracil is the classic example of a cycle-specific S-phase-dependent drug with a short half-life (10 to 20 minutes).[40] It is therefore reasonable to postulate that conventional bolus injection may not be the most effective administration schedule for this drug. UFT is composed of 1-(2-tetrahydrofuryl)-5-fluorouracil (ftorafur [Tegafur]) and uracil in a molar ratio of 1:4. It is an orally available agent that appears to have activity comparable to intravenously administered 5-FU in combination with leucovorin.[35-39] Thus, the introduction of oral UFT may allow for the administration of long-term low-dose oral 5-FU with the same pharmacokinetic profile as a continuous IV infusion.

In our new study, we plan to substitute weekly oral UFT plus leucovorin for high-dose 5-FU plus folinic acid. Oral UFT given daily for 14 days allows for prolonged exposure to the drug without the need for a central catheter or an infusion pump. Considering the clinical and experimental data described above, the combination of paclitaxel plus UFT and leucovorin warrants investigation as salvage chemotherapy in metastatic breast cancer. Therefore, the appropriate dose schedule for this combination is being determined in a phase I study, which started in May 1997. Finally, it would also be of interest to see a randomized comparison of oral UFT and/or continuous 5-FU infusion in combination with paclitaxel vs conventional schedules as first-line chemotherapy for the palliation of advanced breast cancer. Such a trial should include toxicity and quality-of-life measures in addition to the usual efficacy end points.

References:


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