UFT in the Treatment of Colorectal and Breast Cancer

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UFT and leucovorin (Orzel) is a combination of tegafur and uracil in a molar ratio of 1:4. Tegafur, a prodrug of 5-fluorouracil (5-FU), is converted to 5-FU by the hepatic cytochrome P450 pathway, whereas uracil enhances the

Introduction

Breast cancer is the most common malignancy in women in the United States and second only to lung cancer as a cause of cancer death. Based on American Cancer Society estimates, there were 180,300 new cases of breast cancer and 43,900 deaths from breast cancer in 1998 in the United States alone. Colorectal cancer is the third leading cause of cancer mortality both in male and females in the United States, with an estimated 131,600 new cases and 55,500 deaths in 1998.[1]

The pyrimidine analogue 5-fluorouracil (5-FU) has been a mainstay of chemotherapy for breast cancer, colorectal cancer, and other malignancies for more than 30 years since its initial synthesis by Heidelberger. Combination regimens such as CAF (cyclophosphamide, doxorubicin [adriamycin], and 5-FU) and CMF (cyclophosphamide, methotrexate and 5-FU) are among the standard therapies for breast cancer. 5-FU is the most widely prescribed therapy for the treatment of advanced colorectal cancer and, combined with leucovorin, is the only currently recommended regimen for use as adjuvant therapy.

5-FU and UFT

An understanding of the mechanism of action of 5-FU has resulted in significant therapeutic advances in the past 10 years, including synergy with leucovorin and low-dose continuous infusion for improving both the antitumor activity and the toxicity profile.

The cytotoxic effects of 5-FU are a result of interference with both RNA and DNA structure and function. 5-FU is converted intracellularly to FdUMP (5-fluoro-2'-deoxyuridine monophosphate) and FUTP (5-fluorouridine triphosphate). FUTP is incorporated into RNA as a fraudulent base causing errors during RNA processing.[2] FdUMP binds to thymidylate synthetase (TS) with greater affinity than the natural substrate and inhibits production of thymidine monophosphate (dTMP), and thus DNA synthesis.[3] 5-FU is catabolized rapidly in the liver by dihydropyrimidine dehydrogenase (DPD) and subsequently excreted in the urine as a-fluoro--alanine (FBAL).[4] Dihydro- pyrimidine dehydrogenase is the initial rate-limiting enzymatic step in the catabolism of pyrimidines,[5,6] and is widely distributed in many tissues, including the liver, lung, gastrointestinal tract, kidney, and many tumors.[7] DPD occupies an important position in the overall metabolism of 5-FU, converting over 85% of clinically administered 5-FU to 5-FUH2, then FBAL. There is a broad variation in DPD activity from person to person, which is partly responsible for great variation in the t1/2 and bioavailability of 5-FU.[8] DPD activity in the intestinal mucosa and liver also contributes to the limited and erratic bioavailability of orally administered 5-FU, and clearance of the drug. The variable DPD activity level of different tumors may contribute to the variable tumor response to 5-FU. In addition, elevated levels of DPD in many tumors after 5-FU treatment may contribute to the development of drug resistance.[9]

When the value of low-dose continuous infusion of 5-FU was confirmed,[10] it was recognized that the requirement for surgically-implanted venous access and need for a constant-infusion pump may impose serious financial and quality of life constraints. Accordingly, the potential for oral administration as a substitute for continuous exposure of fluoropyrimidines has been re-examined.

The oral chemotherapy agent UFT is a combination of uracil and tegafur in 4:1 molar ratio. Tegafur
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(1-[2-tetra hydrofuranyl]-5-FU, ftorafur, BMS-200604) acts as a prodrug of 5-FU, being rapidly and completely absorbed after oral administration, and slowly metabolized by cytochrome P450.[11-13] Uracil is a normal substrate for DPD, which competitively inhibits the metabolism of 5-FU, thereby reducing 5-FU clearance and increasing plasma and intratumor 5-FU concentration.[14] In preclinical studies, the antitumor activity of tegafur is enhanced by co-administration of uracil and this effect is maximized at a uracil:tegafur molar ratio of 4:1. The ratio of 5-FU in tumor tissue compared with plasma or normal tissue is enhanced.[15,16]

In a further effect to maximize the therapeutic efficacy of tegafur, UFT in the United States has been developed in combination with oral leucovorin (calcium folinate), a derivative of tetrahydrofolic acid. Leucovorin increases the reduced folate concentration, stabilizing the FdUMP-TS complex and therefore further enhancing 5-FU effects to mimic the biochemical modulation of 5-FU with leucovorin.[17]

Phase I studies of UFT in the United States have examined two schedules: 5 days of drug administration repeated every 21 days, and 28 days repeated every 35 days. The daily dose of UFT is given in 3 daily doses, every 8 hours.[18,19] Granulocytopenia is dose-limiting with the 5-day schedule, while diarrhea is the principal toxicity seen with 28-day dosing. The dose of 350-400 mg/m²/day in a 28-day schedule has been recommended for phase II trials as a single agent. Further phase I studies have concentrated on UFT plus leucovorin (Orzel). Four large institutions in the United States conducted similar phase I trials of UFT plus leucovorin on 14-day and 28-day schedules, at 8 hour intervals (Table 1).[18-22] Diarrhea, nausea, and vomiting are dose-limiting. These investigators have recommended a UFT dose of 350 mg/m²/day with various doses of leucovorin (15-150 mg/day) for further combination studies.

**UFT in Colorectal Cancer Treatment**

**Phase II Studies of UFT in Colorectal Cancer**

Starting in 1993, several phase II trials of UFT (tegafur/uracil) and leucovorin have been conducted in the United States. All patients enrolled in these trials had measurable diseases and no prior chemotherapy for metastatic colorectal cancer.

With the initial regimen of UFT 350 mg/m²/d and leucovorin 150 mg/d, five of the first seven patients at the M. D. Anderson Cancer Center developed grade 3 diarrhea. Subsequently, 39 patients were treated with UFT at 300 mg/m²/d and leucovorin at 150 mg/d.[23] The lower dose was associated with less grade 3 diarrhea. No significant neutropenia, thrombocytopenia, hand-foot syndrome, mucositis, or alopecia was seen. Another phase II trial at the University of Southern California and Memorial Sloan-Kettering Cancer Center treated 21 patients with advanced colorectal cancer with UFT 350 mg/m²/d plus 15 mg/d of leucovorin.[22] The toxic effects of these two doses of UFT are presented in Table 2.

One complete response (CR) and 15 partial responses (PR) were achieved in the 39 patients treated with the 300 mg/m²/d regimen; the median survival was 16 months. The overall response rates of these phase II trials ranged from 26% to 44% (Table 3).

Subsequent trials of UFT and leucovorin have used a leucovorin dose of 75 or 90 mg/d (25 mg or 30 mg every 8 hours), because of the saturable oral absorption of leucovorin when the dose exceeds 25 mg.[24]

A phase II trial of UFT and leucovorin was conducted in Europe with UFT at 390 mg/m²/d and leucovorin (either 30 mg/day oral for 14 days or 500 mg/m² IV on day 1) in 75 advanced colorectal cancer patients. This regimen resulted in an overall response rate of 39%.[25] The patients in the phase II studies from Europe and the United States are compared in Table 4.

In Spain, the Oncopaz clinical trial evaluated UFT plus leucovorin in elderly patients with advanced colorectal cancer (median age 74 years).[26] They observed an overall response rate of 29%, with diarrhea as the major toxicity. UFT plus leucovorin was felt to be both well-tolerated and feasible as
outpatient treatment for elderly patients.

The efficacy of UFT with leucovorin was demonstrated in a separate phase II study in patients with metastatic rectal carcinoma.[27] Patients were treated with UFT at 600 mg/m²/d and leucovorin at 90 mg/d for 14 days in a 28-day schedule. Of the 52 evaluable patients, 50% had liver metastases, and 62% had received treatment for advanced disease prior to the trial. Overall response was 70% in patients without previous chemotherapy, and 22% in patients who had had previous treatment. The median time to progression for all patients was 8.2 months, but was 19.6 months in patients without prior chemotherapy.

Phase III Trials in Colorectal Cancer

Based on the results from phase II trials, two large phase III trials were conducted of UFT/leucovorin (Orzel) as first-line treatment for metastatic colorectal cancer.[28,29] These trials compared oral UFT plus leucovorin vs a 5-day intravenous bolus regimen of 5-FU (Mayo Regimen) at 425 mg/m²/d and leucovorin at 20 mg/m²/d every 4 or 5 weeks for trial 011 and every 5 weeks for trial 012. The trials used UFT at 300 mg/m²/d with leucovorin at 75 to 90 mg/d (in Canada and Europe, the leucovorin dose was 90 mg/d), with both drugs given in three daily doses at 8-hour intervals for 28 days in a 35-day schedule. The trials were stratified for performance status, measurability, prior adjuvant therapy, and institution. The primary end point of each trial was survival, and the secondary end point was time to progression (TTP).

**Trial 011:** The results of 011 trial were first presented at the 1999 annual meeting of the American Society of Clinical Oncology (ASCO). Of 816 patients accrued, 409 were randomized to the UFT/leucovorin arm, and 407 to the 5-FU/leucovorin arm. The pretreatment characteristics were equivalent (Table 5). Treatment with UFT/leucovorin produced comparable efficacy to the IV 5-FU/leucovorin (Mayo) regimen. The median survival was 12.4 months (95% CI, 11.2-13.6 months) in the UFT/leucovorin arm and 13.4 (95% CI, 11.6-15.4 months) in the 5-FU/leucovorin arm (P = 0.65). The overall response rate was 12% (48/409) in the UFT/leucovorin arm and 15% (59/407) in the 5-FU/leucovorin arm (P = 0.232).

UFT/leucovorin was associated with significant improvements in safety compared with the 5-FU/leucovorin regimen. UFT treatment resulted in fewer and less severe toxicities, both hematologic and nonhematologic, including gastrointestinal and hand-foot syndrome (Table 6 and Table 7). The study also showed fewer concomitant medications were needed for side effects in the UFT/leucovorin arm (Table 8). Dose reduction and dose delays were necessary less often in the UFT/leucovorin arm than in the IV 5-FU/leucovorin arm (Table 9).

Since UFT was administered orally, compliance was evaluated in the study. More than 89% of patients were compliant at a level of 90% or higher, and more than 99% of patients complied at a level greater than 80%.

**Trial 012:** In the 012 study, 380 patients were accrued with 190 patients in each arm. The median survival was 12.3 months (95% CI, 10.4-13.8 months) in the oral UFT/leucovorin arm and 10.3 months (8.2-13.0 months) in the IV 5-FU/leucovorin arm. The overall response rate was 11% (20/190) in the UFT/LV arm and 9% (17/190) in the 5-FU/leucovorin arm (P = 0.593). The toxicity profile was similar to that of the 011 study.

Both large phase III trials demonstrated that oral UFT/leucovorin as initial treatment for metastatic colorectal cancer produces equivalent survival to intravenous 5-FU and leucovorin (Mayo regimen). Clinically, oral UFT and leucovorin appears to have significant safety advantages including less severe myelosuppression, febrile neutropenia, infection, severe stomatitis/mucositis, diarrhea and nausea/vomiting, hand-foot syndrome, and concomitant medication use.

**Adjuvant Treatment in Colorectal Cancer**

Efficacy of UFT as adjuvant chemotherapy has been studied in Japan for patients with curatively resected colorectal cancer.[30] In one study, 476 patients were randomized to receive mitomycin C
(6 mg/m\(^2\)) 1 day prior to and 1 day following surgery with or without oral UFT (400 mg/day) for 1 year. After a median 3-year follow-up period, the disease-free survival rate increased significantly in the UFT treatment arm compared with the mitomycin alone arm (\(P = 0.026\)). These preliminary results suggest that UFT may be valuable as an adjuvant chemotherapy agent in prolonging disease-free survival in resectable colorectal cancer patients.

In the United States, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has completed protocol C-06, which examined a 28-day schedule of UFT/leucovorin vs a weekly regimen of intravenous 5FU/leucovorin as adjuvant therapy in stage II/III colon carcinoma. UFT was given at 300 mg/m\(^2\)/d with oral leucovorin at 90 mg/d for 5 cycles. The intravenous regimen administered was as follows: 5-FU at 500 mg/m IV bolus and leucovorin at 500 mg/m IV over 2 hours weekly for 6 weeks out of 8, for 3 cycles. Accrual was completed by December of 1999, and results are pending.

**UFT Approval as a First-line Treatment for Advanced Colorectal Cancer**

UFT/leucovorin (Orzel) has been submitted to the United States Food and Drug Administration (FDA) for approval as a first-line treatment of advanced colorectal cancer. On September 16, 1999, the FDA’s Oncologic Drug Advisory Committee unanimously agreed that the oral therapy with UFT capsules plus leucovorin calcium tablets was equivalent to the Mayo Clinic regimen of 5-FU/LV in terms of survival in the treatment of metastatic colorectal cancer, as documented in the two clinical trials presented.

As of this writing, approval by the FDA is still pending, with two issues needing resolution. First, there is concern at the FDA that the drug was not truly equivalent to the Mayo Clinic regimen of 5-FU/LV. Although both the 011 and 012 trials are comparable, the schedule of the 012 trial was every 5 weeks instead of the standard Mayo regimen of every 4 weeks initially for 2 cycles, followed by 5-week cycles. Second, there is also a question about the contribution of uracil to the fixed combination of uracil and tegafur, which comprises Orzel.

From the perspective of a medical oncologist, neither issue seems pivotal. Equivalency cannot always be generalized, and may depend on the type and stage of disease, goal(s) of treatment, and type of treatment. Oncologists and patients may need alternative treatments, especially oral and/or less toxic regimens for many reasons (eg, economic issues, patient selection, and patient’s preference).

Uracil is a natural occurring, nontoxic substance in UFT that inhibits DPD and prolongs the concentration of 5-FU in plasma and tumor cells. The mechanism, toxicity, and molar ratio of uracil combined with tegafur has been well studied [15,16], and there seems to be little reason to go back to repeat these studies.

A more global and relevant issue is that, since the first-line therapy of advanced colorectal cancer is changing to the combination of 5-FU/leucovorin and CPT-11(Camptosar), the overall role of UFT and leucovorin alone remains to be established in standard practice. Phase I/II trials are being conducted in which UFT/leucovorin is being combined with CPT-11 or oxaliplatin and other agents to find more effective regimens for advanced/metastatic colorectal cancer that incorporate both intravenous and oral drugs.

**UFT in the Treatment of Breast Cancer**

UFT also has been studied extensively for breast cancer as an adjuvant for primary cancer and as palliative treatment for metastatic disease. These trials were based on the antitumor efficacy of 5-FU in breast cancer treatment.

**UFT/Leucovorin in the Treatment of Advanced/Metastatic Breast Cancer**

The prognosis for patients with advanced breast cancer who fail a first-line chemotherapy regimen remains poor. Currently, second-line management with various combination regimens seems to be primarily palliative, with response rates of 20% to 40%. These regimens are not curative and may be
associated with considerable toxicity.

Pooled data from a Japanese phase II study showed the response rate of UFT in a subset of patients with advanced breast cancer was 32%. The efficacy of UFT as a single agent has also been demonstrated in several other phase II studies in patients with advanced metastatic breast cancer. One Japanese study compared the efficacy of UFT vs tegafur in 56 patients (UFT 400 mg/day vs tegafur 800mg/day, 28 patients in each arm).[33] The overall response rate in the UFT arm was 40% (CR 11%, PR 29%) and 21% (CR 7%, PR 14%) in the tegafur arm.

In a study conducted by Daniels et al, 70 heavily pretreated patients were given UFT 10 mg/kg/d. Overall response rate was 24% (2% of CR and 22% of PR).[34] Another study evaluated UFT plus leucovorin in 29 heavily pretreated (including anthracycline, paclitaxel, and vinorelbine) advanced breast cancer patients. Doses of 300 mg/m2/d of UFT and 45 mg/d of leucovorin were given every 12 hours. This combination achieved a 25% response rate (8% CR, and 17% PR).[35]

A randomized trial compared the efficacy of UFT vs intravenous 5-FU, given in combination with AC (Adriamycin and cyclophosphamide) at the Philippines General Hospital.[36] In this study, patients received either oral UFT (350 mg/m2/d, days 1 to 14, n = 31) or IV 5-FU (500 mg/m2/d 1 and day 8, n = 31), in combination with doxorubicin (50 mg/m IV day 1) and cyclophosphamide (500 mg/m IV day 1). The overall response rate was 48.4% in UFT plus AC arm and 35.5% in 5-FU plus AC arm (P = 0.30).

The median response duration was 16 weeks (range 4 to 30 weeks) for both arms. The median overall survival was 12 months for the UFT plus AC arm and 11 months for the 5-FU plus AC arm. Anemia and stomatitis were significantly more common in the 5-FU arm (P = 0.02). This trial shows that the response rates, duration of response, and survival with oral UFT are comparable to those with intravenous 5-FU in a combination chemotherapy regimen for advanced breast cancer.

A study combining cyclophosphamide (65 mg/m orally on days 1-14), doxorubicin (30 mg/m IV on day1), and tamoxifen 20 mg/d orally on days 1-21 with UFT (300 mg/m on days 1-14) for 20 patients with recurrent breast cancer produced an overall response rate of 58% (95% CI, 29% to 87%). Adverse events (> CTC grade 3) included leukopenia in six patients, anemia in one patient, and generalized malaise in one patient.[37] There are several ongoing studies evaluating UFT/leucovorin combined with paclitaxel/vinorelbine.[38,39]

All of these studies have shown promising evidence of the activity of UFT in treating advanced breast cancer. However, most have been conducted by single institutions, and with relatively few patients. Large and multicenter studies are needed to definitively prove efficacy.

**UFT in Stage II Breast Cancer**

Two large studies have evaluated UFT as adjuvant treatment for stage II breast cancer. Hokkaido Adjuvant Chemoendocrine Therapy for Breast Cancer (ACETBC) Study Group randomized stage II estrogen-receptor (ER) positive patients to two treatments.[40] All patients received mitomycin intravenously at 13 mg/m on the day of surgery. In arm A, patients received oral tamoxifen only, at 20 mg/d, 14 days after surgery for 2 years (n = 219). In arm B, patients received UFT 400 mg/d plus tamoxifen 20 mg/d (n = 225). There was no difference in the 5-year survival rate (93% in arm A vs 95.4% in arm B). However, the 5-year relapse-free survival rates were 83.1% for arm A and 90.7% for arm B, a significant advantage for the UFT plus tamoxifen arm (P = 0.02).

The Nishinihon Cooperative Study Group of Adjuvant Therapy for Breast Cancer evaluated a similar regimen. A benefit from the mitomycin, UFT, and tamoxifen combination was suggested in premenopausal ER-positive patients.[41]

UFT in the neoadjuvant setting for Stage IIIb breast cancer has also been investigated. In an ongoing phase I/II trial, 11 patients with stage IIIb disease have been enrolled, with a fixed dose of doxorubicin (60 mg/m IV bolus) and paclitaxel (200 mg/m IV 3-hour infusion) with escalating UFT doses of 200, 250, 300, 350 mg/m/d in a 21-day schedule. With nine evaluable patients, two patients have had complete responses, and the other seven had partial responses. A mastectomy was
Summary

UFT plus leucovorin has been shown to be a convenient, well-tolerated, and effective treatment regimen for advanced colorectal cancer. It has also shown promise in the treatment of breast cancer as both adjuvant or palliative therapy. Although the combination of oral UFT/leucovorin had shown equivalent efficacy for advanced colorectal cancer in comparison with 5-FU/leucovorin, its advantages may be in ease of administration, reduced neutropenia, fewer hospitalizations for toxicity, less oral mucositis, fewer clinic visits, and fewer laboratory tests. There is also less infusion-related side effects, including infection and bleeding. Trials of UFT/leucovorin combined with other cytotoxic agents (eg, CPT-11, oxaliplatin) will provide further information about future optimal treatments for colorectal cancer. Protracted venous infusion of 5-FU is superior to bolus 5-FU when combined with external beam radiation for treating localized rectal cancer.[31] For this reason, UFT is also being studied in patients with rectal adenocarcinoma, as a potential substitute for protracted venous infusion of fluorouracil.

Questions and Answers

Jean Grem, MD: Dr. Haller, in the intergroup study, the monthly scheduled 5-FU-leucovorin was for six cycles and the Roswell Park regimen was four cycles, which ended up being longer than 6 months. My experience is that everybody looks at the abstract, which concludes that approximately 6 months of therapy with 5-FU-leucovorin is the standard. But a lot of people have just been getting three cycles.

Daniel Haller, MD: Actually, it’s 30 weeks, about 7 months. It could be that, in truth, the number of cycles is irrelevant; that the length of time is important.

John Marshall, MD: Why do you think European colon cancer is worse than colon cancer in the United States in regard to response rates? They just always seem to be about 5% to 10% points lower.

Dr. Haller: It partly has to do with how the protocol is written and how people interpret the protocol in terms of taking people off studies. The survivorship doesn’t change a great deal. If your pretest probability is that something’s not working, you look for every excuse to take someone off a trial faster than you will if you believe they’re going to respond. Most people review the responders, but they don’t review the nonresponders who were taken off the study. So it would be interesting, if the finances were there, to go back and look at patients who might have been taken off study prematurely. I think a lot of patients are actually taken off treatments too soon. They are still getting benefit and we take them off for regulatory purposes. So in clinical trials, the time-to-tumor progression is very short, compared to what we typically see in our own practices.

I’m not sure we have the best model for evaluating efficacy. I still think progression-free survival is the most sensitive end point, but it’s a misery for drug development, because you’re looking at relatively small intervals. Thus, most companies are unwilling to pick up the cost of the monthly CT scans, which adds another $10,000 per patient. Few, if any, insurance carriers are willing to pay for these frequent markers of response. It’s easy to screen for markers of death or toxicity, but response maintenance or failure of progression is very, very hard.

Leonard Saltz, MD: I’d like to go back to the development of UFT (uracil and tegafur). Basically, M. D. Anderson and Roswell Park together looked at the high-dose schedule and came up with 350 mg/m$^2$/d. Then it was cut back to 300 mg/m$^2$. And when you consider the exquisite sensitivity of leucovorin in terms of infusional regimens, there’s probably an enormous drop in the intensity of the regimen and that may be why we have a very nontoxic regimen.

Paulo Hoff, MD: The dose was not dropped to 300 mg/m just out of the hat. We did start the phase II trial at 350 mg/m and seven out of eight patients had intolerable diarrhea. So that’s when the dose was dropped. The drop of the leucovorin was based on preclinical data showing that if you go above
25 mg of leucovorin, patients are really not absorbing any more.

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