Using Preoperative UFT to Predict Sensitivity to Fluoropyrimidines in Colorectal Cancer

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This study was designed to determine if histopathologic evaluation of patients with resectable colorectal cancer following preoperative chemotherapy with uracil and tegafur with a molar ratio of 4:1 (UFT) could predict

Introduction

Uracil and tegafur (in a molar ratio of 4:1 [UFT]) plus oral calcium folinate make up the compound known as Orzel. Recent experience with this agent suggests a high response rate in metastatic and advanced colorectal cancer.[1] UFT has been commercially available in Japan since 1984 and is now widely used for the adjuvant treatment of gastric, colorectal, and breast cancers. It is administered as a long-term oral agent in mildly toxic, divided daily-dose schedules.[2] Comparison of the activities of long-term oral administration of UFT vs tegafur alone in the treatment of patients with curatively resected colorectal cancer has been carried out in large clinical, randomized, controlled studies in Japan.[3] In these trials, there were no benefits to UFT therapy in 5-year survival, except among the subgroup of patients with Dukes’ C rectal carcinoma.

In our previous study, we attempted to improve survival for 185 patients with operable colorectal cancer by delivering preoperative UFT 600 mg/day for 10 days and postoperative adjuvant UFT 400 mg/day for 12 months.[4] Although administration of preoperative oral UFT yielded no survival benefit, macroscopic changes were noted in resected tissue of some treated patients (Figure 1). Histologic assessment of these tumors revealed moderate histopathologic changes, such as necrosis, loosening of cell-to-cell contact, and vacuolation of nuclei. On reexamination of tumor samples, it was shown that 22.2% of 126 UFT-pretreated colorectal cancer patients had moderate or marked tumor histology changes (grades 2 or 3), whereas only one of 48 nontreated patients (2.1%) showed a moderate cellular change (Table 1).

Based on these findings, we theorized that histopathologic changes following preoperative UFT chemotherapy might predict chemosensitivity to fluoropyrimidines. To test this hypothesis, we designed a controlled trial specifically to assess the predictive value of histopathologic changes associated with preoperative UFT chemotherapy for sensitivity to postoperative adjuvant fluoropyrimidine-based therapy in patients with resectable colorectal cancer.

Patients and Methods

Eligibility
Eligibility was based on the following characteristics: 1) histologically proven colorectal cancer; 2) potential for complete resection; 3) early cancer excluded; 4) < 75 years of age; and 5) written informed consent.

Preoperative Chemotherapy
The preoperative chemotherapy regimen included oral UFT 600 mg/day (200 mg three times daily) administered for at least 10 days prior to surgery.

Histopathologic Assessment
Resected tumors were stained by routine hematoxylin and eosin (H&E). Histopathologic effects at the maximum section (center) of the tumor were estimated by the amount of necrosis or total amount of tumor disappearance. These effects were then categorized into four categories, including two subcategories for grade 1: Grade 0 represents no change, where neither necrosis nor cellular change can be seen throughout the lesion. Grade 1A describes necrosis or tumor reduction in less than one third of the lesion; grade 1B represents necrosis or tumor reduction in no more than two
thirds of the lesion. Grade 2 indicates a moderate change marked by necrosis or disappearance of tumor in more than two thirds of the lesion, with viable tumor cells remaining. Grade 3 describes a pathologic complete response, leaving no observable viable tumor cells. Figure 2 illustrates (at 20 × magnification) a typical case of grade 2 tumor changes involving necrosis or disappearance of more than two thirds of the lesion, with viable tumor cells remaining. Figure 3 is a high-powered view of a grade 2 tumor response, delineating vacuolation of cancer cells and loosening of cell-to-cell contact.

**Randomization Procedures**

Before randomization, patients were stratified according to tumor site (ie, colon or rectum) and results of histologic grading (ie, grade ≥ 2 [sensitive group] and grade ≤ 1B [nonsensitive group]). Patients from both the sensitive and nonsensitive groups were then randomly assigned to either postoperative adjuvant chemotherapy with UFT 400 mg/day (200 mg twice daily) for 12 months, or no treatment (Figure 4).

**Statistical Methods**

Survival and recurrence curves were calculated using the standard Kaplan-Meier methodology. Log-rank statistics were used to compare survival distributions.

**Results**

A total of 152 patients were entered in this trial, among whom 78 had colon cancer and 74 had rectal cancer. UFT was administered preoperatively to a mean total dose of 7.76 g ± 3.27 g. At the time of analysis, 13 patients (8.6%) were ineligible (five colon cancers and eight rectal cancers), leaving 139 patients available for evaluation.

On histologic grading, 13 cases (9.4%) were grade 0, 72 cases (51.8%) were grade 1A, 32 cases (23.0%) were grade 1B, and 22 (15.8%) were grade 2. There were no grade 3 cases. Twenty-two (15.8%) cases were stratified into the sensitive group and 117 (84.2%) cases were stratified into the nonsensitive group. From the 22 sensitive cases, 13 cases were randomly assigned to adjuvant chemotherapy, and nine to no adjuvant chemotherapy. From the 117 nonsensitive cases, 60 cases were randomly assigned to adjuvant chemotherapy and 57 to no treatment (Table 2). There were no significant differences in preoperative patient characteristics or surgical findings between the two study groups.

**Toxicity**

There were no toxicities or operative complications related to preoperative chemotherapy. No severe (grades 3 or 4) toxicities related to postoperative adjuvant chemotherapy occurred.

**Patient Survival and Disease-Free Rates**

Patient survival and disease-free rates are illustrated in Figure 5 and Figure 6. Among pretreatment nonresponders, 3-year survival rates were 87.6% in the adjuvant-chemotherapy group and 84.9% in the no-chemotherapy groups (no significant difference). Among responders, 3-year survival rates were 100% in the adjuvant-chemotherapy group and 62.5% in the no-chemotherapy group (P = .0351). Three-year disease-free survival rates among nonresponders were 81.7% and 80.1%, with and without adjuvant chemotherapy, respectively. For responders, the 3-year disease-free survival rates were 100% among patients receiving adjuvant chemotherapy and 60.0% in the no-treatment group (P = .0715).

**Discussion**

In Japan, UFT, either alone or in combination with mitomycin C (Mutamycin), has been evaluated as adjuvant chemotherapy for colorectal cancer following curative resection.[5,6] In our previous randomized, controlled study, we tested for evidence of a survival benefit when preoperative chemotherapy with UFT 600 mg/day for 10 days was combined with postoperative adjuvant chemotherapy (UFT 400 mg/day for 12 months).[4] Unfortunately, there was no survival advantage associated with preoperative use of UFT; 5-year survival rates were 76.9% among 92 patients preoperatively treated with UFT and 82.4% in 93 patients who did not receive preoperative chemotherapy. However, remarkable macroscopic changes were observed in resected tissue from some patients who had received 10 days[] preoperative oral UFT therapy. Histologically, these changes included ballooning or vacuolation of cells, pyknosis of nuclei, degradation or disorganization of glandular structures, necrosis of cells or tissue, disappearance of cells, granuloma formation (including histiocytic aggregation), and fibrosis with or without myxoid change.

On histopathologic reexamination, 25 of the 126 (20.0%) UFT-pretreated patients showed evidence of moderate cellular changes (grade 2), and three patients (2.4%) showed histopathologic complete response (grade 3) at maximum section. In 48 patients who received no adjuvant chemotherapy,
only one patient (2.1%) exhibited grade 2 changes (estimation pathologist did not know preoperative chemotherapy status). These findings suggest that histologic changes during preoperative chemotherapy may serve as a chemosensitivity test in vivo for patient response to fluoropyrimidine-based therapy.

There have been other well-known in vitro chemosensitivity tests, such as the succinate dehydrogenase inhibition (SDI) assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assay, and human tumor clonogenic assay (HTCA).[7,8] These assays, however, are complicated and have a low cost-benefit ratio. Preoperative UFT administration, on the other hand, has low toxicity, requires only H&E staining and histologic estimation, and is considered a safe and cost-effective in vivo analysis.

In the present randomized, controlled study, we attempted to determine if histologic gradings after pretreatment with UFT could predict response to postoperative adjuvant chemotherapy. Our 3-year disease-free and overall survival rates were 100% among patients considered histopathologically sensitive (grade ≥ 2); three of the nine patients in the sensitive group who did not receive adjuvant chemotherapy died. There was no significant difference in disease-free and overall survival rates between treatment groups among nonsensitive patients.

**Conclusion**

We conclude that histopathologic analysis to determine response to preoperative UFT chemotherapy can predict sensitivity to fluorouracil-based treatment, enabling directed postoperative adjuvant chemotherapy to sensitive patients. In our present study, grade ≥ 2 sensitivity was observed in 15.8% of patients—a rate similar to the response rate observed with conventional fluoropyrimidine or UFT treatment.[2] We believe that grade 1B patients (23.0%) may respond to a modulated fluoropyrimidine (Orzel), such as UFT plus oral calcium folinate. Treatment with other drugs, such as irinotecan and oxaliplatin, should also be considered for patients with grades 0 and 1A response to preoperative UFT.[9,10]

**References:**


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