A Phase I Study of oral UFT Given Concomitantly with Standard Preoperative Radiotherapy for Rectal Cancer

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Abstract

Background: Preoperative radiotherapy is standard treatment for rectal cancer and is often combined with 5-fluorouracil-based chemotherapy. UFT, a new oral 5FU derivative, given daily during a course of radiotherapy mimics the effect of continuous-infusion 5FU.

Objectives: To determine the maximum tolerated dose of oral UFT and leucovorin with preoperative pelvic irradiation for rectal cancer, and assess tumor response.

Methods: In this phase 1 trial, 16 patients aged 42–79 years with tumors within 12 cm of the anal verge received radiotherapy, 45 Gy over 5 weeks, an escalating dose of oral UFT, and a fixed dose of 30 mg/day leucovorin. UFT and leucovorin were given for 28 consecutive days concomitant with the first 4 weeks of radiotherapy. Surgery was scheduled for 4–6 weeks after completion of radiotherapy. The surgical procedure was determined by the surgeon at the time of surgery.

Results: No grade III toxicity was seen at 200 mg/m^2/day UFT. Of eight patients who received 240 mg/m^2/day UFT, one developed grade IV diarrhea; of four patients who received 270 mg/m^2/day UFT, one was hospitalized with grade IV diarrhea and leukopenic fever and died during hospitalization. Of the 15 evaluable patients, 9 had pathologic tumor downstaging including 4 patients with complete response. Only one patient required a colostomy.

Conclusions: The MTD of UFT together with leucovorin and preoperative radiotherapy for rectal cancer is 240 mg/m^2. The major toxicity was diarrhea. Downstaging was noted in 60% of patients, allowing sphincter-preserving surgery even in patients with low tumors.

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For many years our policy has been to offer preoperative radiotherapy to rectal cancer patients with T3-4 lesions and to patients with low T2 lesions in whom downstaging may facilitate sphincter-sparing surgery. We prefer preoperative to postoperative radiotherapy since it may be less toxic and has the added benefit of allowing tumor downstaging, thereby enabling more patients to undergo conservative surgery. A meta-analysis of 14 randomly controlled trials found significantly improved overall survival and cancer-specific survival for rectal cancer patients receiving preoperative irradiation as compared to those receiving surgery alone [1]. Short course preoperative radiotherapy using large fractions followed by early surgery improves local control and survival [2], but at a cost of perioperative [3] and long-term morbidity and mortality [4,5]. The use of standard fractionation in the preoperative setting with surgery delayed for 4–6 weeks has the advantage of allowing more time for tumor shrinkage and downstaging, which may increase the chances for sphincter-sparing surgery [6]. This prolonged time sequence may also diminish the normal tissue toxicity and perioperative morbidity.

Randomized studies have shown that the addition of 5-fluorouracil-based chemotherapy to postoperative radiotherapy improves local control and survival of rectal cancer patients [7]. This is reflected in the National Institutes of Health consensus statement advocating postoperative chemoradiation for locally advanced rectal cancer [8]. The benefit of adding chemotherapy to preoperative radiotherapy is less well established.

Several groups have demonstrated tumor downstaging in a large number of patients receiving preoperative radiotherapy with 5FU-based chemotherapy for locally advanced rectal cancer [9]. No randomized study using modern radiotherapeutic techniques with or without concomitant 5FU-based chemotherapy has been published, although the results of a large EORTC (European Organization for Research and Treatment of Cancer) study intended to answer this question are eagerly awaited [10].

For patients with rectal cancer who receive postoperative radiotherapy, continuous-infusion 5FU results in improved survival and reduced loco-regional failure compared to a weekly 5FU bolus [11]. The optimal schedule of 5FU-based chemotherapy with preoperative radiotherapy has not been defined. When compared to once a week 5FU injection or 5 consecutive days of 5FU each month, daily continuous 5FU has the advantage of achieving a constant level of radio-sensitizing drug during the radiation course. This regimen has been shown to be well tolerated and results in downstaging of a large percentage of rectal cancers [12,13].

A major limitation to the use of continuous-infusion 5FU is the need for prolonged venous access, which requires either hospitalization or the use of an ambulatory infusion pump, both of which increase the cost of treatment. UFT, a combination of tegafur, an orally absorbed derivative of 5FU and uracil in a 4:1 ratio, is one of several recently available oral fluoropyrimidines. The pharmacokinetic profile of UFT is similar to that of continuous-infusion 5FU [14]. In patients with metastatic colorectal cancer, UFT with leucovorin is as efficacious as intravenous 5FU with leucovorin and is associated with less overall toxicity [15,16]. We therefore embarked on a phase I trial to determine the maximum tolerated dose and the efficacy of UFT with preoperative pelvic radiation for rectal cancer.

Patients and Methods

Eligible for this study were patients aged 18 or more with

5FU = 5-fluorouracil
MTD = maximum tolerated dose

histologically confirmed rectal adenocarcinoma, clinical stage T3-4 up to 12 cm from the anal verge or with low T2 tumors up to 6 cm from the anal verge, and with no evidence of distant metastases. Also required were ECOG performance status 0-1, ability to undergo surgical resection and adequate hematologic function (granulocytes >1,500/ml, platelets >100,000/ml), hepatic function (serum bilirubin and transaminases <1.5 times upper limit of normal) and renal function (serum creatinine <1.5 mg/dl). Patients with hemoglobin <12 g/dl were eligible after receiving blood transfusion before treatment. Patients who had received prior chemotherapy or pelvic radiotherapy, patients with another malignancy in the preceding 5 years, and patients with a history of ulcerative colitis or Crohn's disease were not eligible. The protocol was approved by the hospital's ethical review committee and all patients gave written informed consent prior to participation. Pretreatment evaluation included medical history and physical examination, complete blood count, liver and kidney function tests, colonoscopy and biopsy, abdomino-pelvic computerized tomography, trans-rectal ultrasound and chest X-ray. Patients were assessed at least once a week by one of the study physicians and twice weekly by a radiotherapy nurse. Patients were provided with a diary to record actual oral chemotherapy intake and were instructed to visit a radiotherapy nurse or physician on the onset of any gastrointestinal symptoms. Complete blood count was obtained weekly.

The primary objectives of this study were to determine the maximum tolerated dose of oral UFT given together with leucovorin and preoperative pelvic radiotherapy in patients with rectal cancer and to assess the toxicity of this combination. The secondary objective was to assess response as determined by trans-rectal ultrasound, performed prior to chemoradiation and repeated prior to surgery, and by pathologic staging compared to pre-therapy clinical staging.

All patients received a 45 Gy dose of radiotherapy in 1.8 Gy daily fractions 5 times per week for 5 weeks. The dose was prescribed to the isodose encompassing the primary tumor and the internal iliac nodes (typically the 95% isodose) using 6 or 15 MV photons. Radiotherapy was given with the patient prone, using a posterior field and left lateral and right lateral wedged fields. The small bowel was imaged with barium and a belly board was used in patients who had a large volume of small bowel in the lateral simulation field. Weighting was adjusted individually. The cranial border of the radiotherapy field was placed at the L5/S1 interface and the caudal border was at least 4 cm below the distal edge of the tumor or below the obturator foramina, whichever was lower. The lateral borders of the posterior field were 1.5 cm lateral to the margins of the bony pelvis. The lateral fields included the entire sacrum and coccyx, and the anterior border was planned to the middle of the symphysis pubis in order to include the internal iliac but not the external iliac nodes.

Chemotherapy consisted of escalating doses of oral UFT divided into three daily doses together with a fixed dose of 15 mg oral leucovorin twice daily. UFT and leucovorin were given for 28 continuous days (including weekends) concomitant with the initial 4 weeks of the 5 week radiotherapy course. The starting dose of UFT was 200 mg/m^2/day per os in three divided doses. The second level was 240 mg/m^2/day; the third level was 270 mg/m^2/day and a planned maximum dose level of 300 mg/m^2/day, which is the recommended dose of UFT given for 28 consecutive days with leucovorin and no radiotherapy. The dose of radiotherapy and leucovorin was not increased.

Escalation of the UFT dose was permitted if the first three patients completed preoperative chemoradiation and reached the time for surgery (4 weeks after completing chemoradiation) without a dose-limiting toxicity. If one of the initial three patients at a given dose level developed a DLT at least three more patients were treated at that dose level, and if no more than one of six patients had a DLT the dose was escalated. Additional patients were accrued at the current dose level until the initial three or six patients at each dose level had completed chemoradiation and reached the time for surgical resection. Surgical resection was planned for 4–6 weeks after completion of radiotherapy. The surgical technique was left to the discretion of the surgeon at the time of operation, with the aim of performing a sphincter-preserving procedure whenever possible.

Toxicity was recorded according to the EORTC (1994) toxicity criteria. Previous experience with UFT and with 5FU-based chemoradiation for rectal cancer has shown that diarrhea is by far the most likely cause of dose-limiting toxicity. UFT and radiotherapy were withheld at the onset of grade 3 diarrhea (seven or more stools per day, incontinence, or severe cramping) that did not respond to standard oral anti-diarrhea therapy (loperamide). Patients were reassessed every 3–4 days after stopping therapy and both chemotherapy and radiotherapy were reinstated if the grade 3 toxicity resolved. If grade 3 toxicity recurred there was a further treatment break of 3–4 days. The dose-limiting toxicity was defined as the dose of UFT resulting in grade 3 gastrointestinal toxicity or grade 4 toxicity of any kind necessitating a cumulative treatment break of more than 7 days. Following recovery from a DLT, patients could continue treatment with radiotherapy alone after consultation with the principal investigator.

Results

Sixteen patients (11 males, 5 females) aged 42–79 years (median 68 years) participated in this phase I study. Clinical stage was T3 in all patients. TRUS stage was T2 N0 in 2 patients, T3 N0 in 12 patients and T3 N1 in 2 patients. ECOG performance status was 0 in 11 patients and 1 in the remaining 5 patients. Seven patients were receiving medication for hypertension and two patients had a history of ischemic heart disease. None of the patients had diabetes mellitus.

The patients' characteristics are summarized in Table 1. Four patients were treated at level I (UFT 200 mg/m^2/day) with no grade 3 toxicity and no toxicity-related treatment breaks. One of eight patients treated at level II (240 mg/m^2/day) stopped treatment after 26 days (total radiotherapy dose 3,420 cGy) due to grade 4 diarrhea requiring intravenous fluid replacement. Of the four patients

DLT = dose-limiting toxicity
EORTC = European Organization for Research and Treatment of Cancer
TRUS = trans-rectal ultrasound
ECOG = Eastern Cooperative Oncology Group

Table 1. Patients' characteristics and response to therapy

Level	Pre-therapy TRUS	Distance from anus	Post-therapy TRUS	Pathologic stage	Surgery
1	T3 N1	11 cm	T1 N1	T1 N1	LAR
	T3 N0	8 cm	T1 N0	T0 N0	LAR
	T3 N1	6 cm	T2 N0	T3 N0 (delayed)	LAR
	T3 N0	11 cm	T3 N1	T2 N0	LAR
2	T2 N0	6 cm	T1 N0	T0 N0	APR
	T3 N0	3 cm	T1 N0	Biopsy T0	Refused
	T3 N0	10 cm	Not done	T3 N1 M1	LAR
	T3 N1	8 cm	T3 N0	T3 N0	LAR
	T3 N0	6 cm	Not done	T3 N0	LAR
	T2 N0	10 cm	T1 N0	T1 N0	LAR
	T3 N0	3 cm	T2 N0	T2 N0	LAR
	T3 N0	10 cm	T3 N0	T2 N0	LAR
3	T3 N1	5 cm	T3 N0	T0 N0	LAR
	T3 N0	9 cm	T3 N0	T3 N0	LAR
	T3 N0	3 cm	T3 N0	T3 N0	LAR
	T3 N0	5 cm	died		

LAR = low anterior resection, APR = abdomino-perineal resection.

treated at level III (270 mg/m^2/day) one was hospitalized after only 16 days of treatment (total radiotherapy dose 2,160 cGy) with grade 4 diarrhea and neutropenic fever; he died 6 days later. The toxicity data are shown in Table 2. After consultation with the hospital's institution review board it was decided to consider the dose of 240 mg/m^2/day as the maximum tolerated daily dose of UFT and to continue with a phase II study at this dose level. No problems with drug compliance were noted.

Nine of 13 patients (68%) who underwent TRUS both before and after chemoradiation had tumor downstaging as determined by TRUS [Table 1]. In seven patients the T stage was lowered and in a further two patients the T stage was unchanged but TRUS nodal staging was reduced from N1 to N0. In six patients the post-therapy TRUS overstaged the tumor compared with surgical stage (including one patient whose TRUS showed a T3 lesion which was found at surgery to be T0). When the two patients who did not undergo post-therapy TRUS were included in response analysis the total pathologic downstaging rate was 9 of 15 patients (60%). Four patients achieved complete pathologic response in the final pathologic specimen. All but one of the 14 patients who underwent surgical resection had sphincter-sparing surgery. Six of these patients had tumors within 6 cm of the anal verge.

All surgery was carried out within 6 weeks of completion of chemoradiation, except for one patient with a low lesion who initially refused surgery after achieving downstaging from T3 to T2 according to TRUS. Two months later his tumor increased in size, a low anterior resection was performed and the tumor was found to be pathologically T3. A second patient who had TRUS-based downstaging of a tumor 3 cm from the anal verge refused surgery. She received additional intracavitary brachytherapy and is free of tumor 18 months after completing treatment. There were no major complications related to the rectal surgery. One patient who underwent a cholecystectomy at the time of tumor resection developed a postoperative infection in the cholecytectomy site.

Discussion

Oral radio-sensitizing chemotherapy is an attractive proposition for many patients receiving radiotherapy. Oral medication is more convenient than intravenous medication and precludes the need for venous access. Daily oral delivery facilitates the continuous presence of radio-sensitizing levels of drug during a course of radiation therapy, possibly enhancing radiation-induced cell kill in the most efficient manner. Studies have shown that most patients prefer oral chemotherapy as long as this does not reduce the chances of anti-tumor response [17]. A serious possible drawback of oral chemotherapy in patients with advanced disease is poor patient compliance [18]; however, during a course of radiation therapy, when the patient visits the hospital five times a week monitoring of compliance is entirely feasible.

UFT and capecitabine are both oral 5FU derivatives that have been widely investigated in the clinic [19,20]. In our study the maximum tolerated dose of UFT, given together with 30 mg leucovorin for 28 consecutive days with 45 Gy pelvic radiotherapy was 240 mg/m^2/day. The MTD was determined following a single fatal toxicity in a patient treated at a dose of 270 mg/m^2/day. Although this was the only patient who suffered a grade 3 or higher toxicity at this dose level, in consultation with the hospital ethics committee it was decided not to accrue further patients at this level. In a study of patients with locally advanced, inoperable tumors of UFT treated with chemoradiotherapy in an attempt to achieve tumor respectability, a higher daily dose of UFT (300 mg/m^2/day) was delivered [21]. Most tumors in this study were downstaged to a resectable state, but the gastrointestinal toxicity necessitated prolonged treatment breaks in about 33% of patients. A previous phase I study administered oral UFT together with 90 mg leucovorin per day on a five times a week schedule during a 5 week course of preoperative radiation for rectal cancer [22]. This study found an MTD of 350 mg/m^2/day, which is a dose intensity of 1,750 mg/m^2/week and a cumulative dose of 8,750 mg/m^2 for the entire 5 week course of chemoradiation. The MTD of our study, 240 mg/m^2/week, is equivalent to a dose intensity of 1,680 mg/m^2/week and a cumulative dose of 6,720 mg/m^2 over the entire course of chemoradiation. It is possible that the weekly dose intensity of

Table 2. Toxicity

Dose level	No. of patients	Diarrhea Grade 1–2	Diarrhea Grade 3–5	Skin Grade 1–2	Skin Grade 3–4	Urinary Grade 1–2	Urinary Grade 3–4	Neutropenia Grade 1–2	Neutropenia Grade 3–4
200 mg/m^2	4	2	0	1	0	1	0	0	0
240 mg/ m^2	8	2	1	1	0	1	0	0	0
270 mg/ m^2	4	1	1	0	0	0	0	0	1

UFT defines the toxicity rather than the cumulative dose over 5 weeks. Alternatively, our single fatality may have had an idiosyncratic response to UFT, resulting in a higher true MTD. Severe diarrhea is rare after only 2,160 cGy of pelvic irradiation even with 5FU-based chemotherapy. In addition, neutropenic fever is extremely rare following chemotherapy with 5FU. Nevertheless, in the adjuvant setting of a curable disease, we felt that it was not justified to continue treatment at this dose level even if the strict stopping rules allowed further patient accrual.

The MTD in our study was 80% of the recommended dose of UFT given with leucovorin without radiotherapy. The recommended dose for a 5 day continuous infusion of 5FU with low dose leucovorin during the first and last week of a course of preoperative radiation, 325 mg/m^2/day [23] or 350 mg/m^2/day [24], is in a similar ratio (77–82 %) to the dose of continuous-infusion 5FU without radiotherapy, 425 mg/m^2/day for 5 days, in the commonly used Mayo Clinic regimen [25]. This is not surprising in view of the similar pharmacokinetic and toxicity profiles of UFT and continuous-infusion 5FU.

In conclusion, this phase I study has defined a recommended daily dose of UFT of 240 mg/m^2 given with leucovorin 7 days a week during the first 4 weeks of a 5 week course of preoperative radiation therapy for rectal cancer. This protocol resulted in tumor downstaging in 60% of patients, and all but one of our patients who underwent surgical resection had sphincter-sparing surgery. We are continuing to accrue patients at this dose level in order to define the toxicity and efficacy of this protocol in a larger cohort of patients.

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