

A Phase II Study of Oral UFT and Leucovorin Concurrently with Pelvic Irradiation as Neoadjuvant Chemoradiation for Rectal Cancer

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Abstract. *Background:* Neoadjuvant chemoradiation with continuous infusion (CI) of 5-fluorouracil (5FU) is widely used in rectal cancer. The aim of this study was to evaluate the use of oral tegafur-uracil (UFT) and leucovorin (LV) instead of CI 5FU. *Patients and Methods:* Patients had resectable T3-4 or low T2 rectal adenocarcinoma. Chemoradiation consisted of pelvic irradiation (45 Gy in fractions of 1.8 Gy) and oral UFT (240 mg/m²/day) and LV (30 mg/day) given during the first 28 days of radiotherapy. *Results:* Thirty-two patients were treated; 81% had T3-4 tumors and 25% had N+ disease. Toxicity, predominantly gastrointestinal, was generally mild. Grade 3 toxicity occurred in only one patient. Pathological down-staging was noted in 13 patients (42%) and pathological complete response in 3 (10%). Sphincter preservation was possible in 71% of patients undergoing surgery. *Conclusion:* Neoadjuvant chemoradiation with oral UFT/LV is well-tolerated and active against rectal cancer. Formal comparison with the current standard treatment is warranted.

Neoadjuvant (*i.e.* preoperative) chemoradiation is gaining increasing recognition as the standard treatment approach in localized rectal cancer. The advantages of this strategy over the postoperative approach include *in vivo* assessment of treatment efficacy, an intact blood supply and thereby enhanced radiosensitivity and drug access to the tumor,

increased rate of sphincter preservation and reduced toxicity (1, 2). Its main disadvantage is the limited accuracy of clinical staging leading to over-treatment of some patients with early stage (T1-2 N0) disease (3).

5-Fluorouracil (5FU) has been shown to act both *in vivo* and *in vitro* as a radiosensitizer. Preclinical data suggest that optimal 5FU radiosensitization requires that 5FU be present after each radiation exposure, the drug's concentration is high enough to yield a direct cytotoxic effect and the duration of 5FU administration should be at least one complete cycle in length (4). In light of the short half-life of 5FU, these prerequisites are achieved by continuous infusion (CI) of the drug. This preclinical hypothesis is supported by clinical data from a randomized phase III study of adjuvant chemoradiation indicating that CI 5FU is superior to bolus 5FU (5). Neoadjuvant treatment with CI 5FU and concurrent radiotherapy achieves pathological complete response rates ranging from 10% to 30% (6, 7). A prospective randomized study showed that preoperative chemoradiation with CI 5FU during the first and fifth week of radiation is superior to the same regimen given postoperatively, both in terms of local control and reduced toxicity (8). Hence, neoadjuvant chemoradiation with CI 5FU is currently considered the standard of care in this disease.

The main drawback of treatment with CI 5FU is the unavoidable need for central venous access devices and portable pumps. Oral fluoropyrimidines are therefore attractive alternatives to CI 5FU. UFT, a member of this family, is composed of uracil and tegafur in a molar ratio of 4:1. Uracil increases the absorption and efficiency of tegafur (a prodrug of 5FU). With daily administration, UFT achieves similar concentrations of 5FU as those obtained with CI 5FU (9).

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Results from two large randomized studies in patients with metastatic colorectal cancer have shown that patients treated with UFT and leucovorin (LV) had similar response rates and survival with less toxicity than patients treated with bolus 5FU/LV (10, 11). The aim of this prospective phase II study was to evaluate the efficacy and toxicity of a combination of oral UFT/LV and standard preoperative pelvic radiotherapy in the treatment of patients with localized rectal cancer.

Patients and Methods

Patients were eligible for this study if they had histologically confirmed localized rectal adenocarcinoma defined as clinical stage T3-4 up to 12 cm from the anal verge or low T2 tumors up to 6 cm from the anal verge with no evidence of distant metastasis, ECOG performance status 0-1, adequate hematological, hepatic and renal function and ability to sign an informed consent and undergo surgical resection.

Pretreatment evaluation included medical history and physical examination, complete blood count (CBC), serum chemistry, colonoscopy and biopsy, chest X-ray, abdominal-pelvic computerized tomography (CT) and trans-rectal ultrasound (TRUS).

Radiotherapy. Radiotherapy consisted of a standard protocol of 45 Gray (Gy) in daily fractions of 1.8 Gy each, 5 times per week for a total of 5 weeks. The dose was prescribed to the isodose encompassing the primary tumor and the internal iliac nodes (usually the 95% isodose) using 6 or 15 MV photons. Radiotherapy was given in the prone position using a posterior field and two lateral fields. The superior field border was at the L5-S1 interface and the inferior border was 5 cm distal to the tumor or including the anal sphincter for tumors in the distal 5 cm of the rectum. The lateral borders of the posterior field were placed 1.5 cm outside the true bony pelvis. The lateral fields included the entire sacrum and the anterior border was placed at the middle of the pubis. The small bowel was imaged with barium and individual blocks were used to reduce its volume in the lateral fields. Patients who had a large volume of small bowel in the lateral simulation field were treated on a belly board.

Chemotherapy. Chemotherapy started on the first day of radiation therapy and consisted of oral UFT 240 mg/m²/day and LV 30 mg/day for 28 consecutive days during the first 4 weeks of the 5-week course of radiotherapy. This represents the maximum tolerated dose as determined in our phase I study (12). During chemoradiation patients were evaluated for toxicity on a weekly basis. CBC was obtained weekly and serum chemistry was done at the onset and at the completion of treatment. Toxicity was recorded according to the National Cancer Institute criteria (13). Chemoradiation was temporarily interrupted in the case of grade ≥ 3 diarrhea or myelosuppression.

Surgery. Prior to surgery, patients were restaged with abdominal and pelvic CT, chest X-Ray and TRUS. Surgery was performed 4-8 weeks after the completion of chemoradiation. The selected surgical procedure, low anterior resection (LAR), abdominoperineal resection (APR) or local excision (LE), was left to the discretion of the surgeon.

Table I. *Patient characteristics.*

Characteristic	No. (%)
Age (yrs)	
Median	69
Range	(44-79)
Gender	
M/F	22/10 (69/31)
Performance status	
0	18 (56)
1	14 (44)
Distance from anal verge	
0-6 cm	15 (47)
>6 cm \leq 10 cm	16 (50)
>10 cm	1 (3)
Clinical stage ^a	
T2N0	6 (19)
T3N0	18 (56)
T3N1	7 (22)
T4N1	1 (3)

^aAccording to pretreatment TRUS.

Tumor response was classified into pCR (pathological complete response), pDS (pathological down-staging), SD (stable disease), LP (local progression) and DP (distant progression). pCR was defined as the absence of viable tumor cells in the resected specimen. pDS, SD, LP and DP were determined by comparing pretreatment clinical TNM stage (defined by TRUS and CT scan) with the pathological stage.

Postoperative adjuvant chemotherapy was given according to the treating physician and was not part of the study protocol.

Results

From June 2001 to September 2003, 32 patients were treated in the study. Their main clinicopathological characteristics at presentation are shown in Table I. The majority of patients were males (69%) and the median age was 69 years (range, 44-79 years). Eighty-one percent had T3-4 tumors and 25% had N+ disease. Almost half the tumors were located at the distal rectum (\leq 6 cm from the anal verge).

Toxicity. All patients were evaluable for toxicity. Chemoradiation was generally well tolerated. Anal pain, nausea and vomiting and diarrhea were the most common side effects, occurring in 44%, 41%, and 37% of the patients, respectively (Table II). Severe toxicity (grade 3 diarrhea) was observed in one patient (3%). Hematological toxicity was minimal. All patients but one, who discontinued therapy due to grade 3 diarrhea after receiving a dose of 36 Gy, completed the full course of radiation as planned.

Efficacy. Clinical response was available for all patients and pathological response was available for the 31 patients

Table II. Toxicity profile.

Type of toxicity	Number ^a	%
Non-hematological toxicity		
Diarrhea		
Grade 1-2	11	34
Grade 3	1	3
Nausea/Vomiting		
Grade 1	8	25
Grade 2	5	16
Anorexia		
Grade 1	4	12
Grade 2	2	6
Radiation dermatitis		
Grade 1	2	6
Grade 2	1	3
Anal pain		
Grade 1	13	41
Grade 2	1	3
Rectal bleeding		
Grade 1	7	22
Abdominal pain		
Grade 1	5	16
Grade 2	1	3
Urinary symptoms		
Grade 1	8	25
Grade 2	1	3
Hematological toxicity		
Anemia		
Grade 2	1	3
Thrombocytopenia		
Grade 2	1	3

^aNumber of patients experiencing toxicity.

undergoing surgery (Table III). pCR was seen in 3 patients (9.7%) and the overall rate of pathological down-staging (pCR + pDS) following chemoradiation was 42%. Four patients (12.4%) had evidence for progression of disease during treatment, 2 who developed LP and 2 who developed liver metastases.

The surgical procedure was LAR in 20 patients (62%), APR in 9 (28%) and LE in 2 (6%). One patient with cDS refused surgery (3%). Overall, sphincter-sparing operations were performed in 22 patients of the 31 undergoing surgery (71%). Tumor down-staging enabled sphincter-preserving procedure in one of the 6 patients (17%) who were initially planned for APR due to the distant location of their tumors.

Discussion

Neoadjuvant chemoradiation with CI 5FU is currently the standard therapy for localized rectal cancer. This treatment has been repeatedly shown to be both effective and safe (6-8).

Table III. Tumor response.

Response	No. (%) ^a
pCR (pathological complete response)	3/31 (10)
pDS (pathological down-staging)	10/31 (32)
SD (stable disease)	14/31 (45)
LP (local progression)	2/32 (6)
DP (distant progression)	2/32 (6)

^aData on pathological response was missing in one patient with clinical down-staging who refused surgery.

However, infusional regimens are time-consuming, inconvenient and uncomfortable for the patient, and require regular hospital visits and sometimes hospitalization. They are also often associated with venous access-related complications such as infection, sepsis, thrombosis and blockage (14). Therefore, efforts have been made to identify alternative strategies to CI 5FU in this setting. The use of oral fluoropyrimidines such as UFT/LV has the potential to represent an appealing alternative.

UFT/LV has already been shown to be equivalent to *i.v.* bolus 5FU/LV in two clinical settings in colorectal cancer, metastatic disease and adjuvant chemotherapy after curative resection of colon cancer. In metastatic disease, two randomized phase III trials demonstrated that patients treated with UFT/LV had similar response rates and survival as those treated with *i.v.* 5FU/LV but the oral treatment was associated with lower toxicity (10, 11). In the adjuvant setting, several studies, including the large NSABP C-06 trial, have shown that oral UFT/LV is equivalent to bolus 5FU/LV, in terms of both patient outcome and toxicity (15-17). In these settings, UFT/LV is currently an acceptable alternative to *i.v.* bolus 5FU/LV.

To date, no randomized comparison between UFT/LV nor any other oral fluoropyrimidine to *i.v.* 5FU in the chemoradiotherapy of rectal cancer, neither pre or post-operatively, has been reported, and data on this setting is derived exclusively from phase I-II studies. In the current trial, neoadjuvant chemoradiation with UFT/LV has led to tumor down-staging in 42% of patients, including a 10% pCR rate. Treatment was well tolerated and safe. These results are comparable to those of 5FU-based protocols of neoadjuvant chemoradiation (18). For example, the German Cooperative randomized study showed an 8% pCR rate in the neoadjuvant arm, with a toxicity profile very similar to ours (8). Our results also resemble those of other studies with UFT-based chemoradiation in rectal cancer that have been recently reported (19-22). In these studies, treatment was usually well tolerated with diarrhea being the most common grade ≥ 3 toxicity and the rates of tumor down-staging and pCR were 54-75% and 9-25%, respectively (19-22).

Conclusion

Considering the available information from all these studies, including ours, it appears that the oral regimens do have the potential to replace the *i.v.* protocols. With similar efficacy and toxicity profiles, the oral regimens seem to offer a more simple and convenient delivery method of 5FU. Nevertheless, a formal comparison with the standard 5FU regimens within the frame of randomized phase III studies is necessary before the standard of care in this disease is altered.

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