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Intravenous 5-Fluorouracil Versus Oral Doxifluridine as Preoperative Concurrent Chemoradiation for Locally Advanced Rectal Cancer: Prospective Randomized Trials

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Background: Preoperative radiation treatment with concomitant intravenous infusion of 5-fluorouracil (5-FU) is known to be effective in shrinking and downstaging of tumors. However, chemotherapy has often been limited by its toxicity and poor patient compliance. Oral 5-FU is known to have several advantages over conventional intravenous 5-FU infusion such as lower toxicity and higher quality of life without compromising the efficacy of the treatment. The aim of this study was to compare intravenous 5-FU with oral doxifluridine with respect to tumor response, toxicity and quality of life.

Methods: Twenty-eight patients with rectal cancer, staged as over T3N1 or T4 by transrectal ultrasonography between July 1997 and December 1998, were included in this study. Intravenous 5-FU (450 mg/m^2) and leucovorin (20 mg/m^2) were given for five consecutive days during the first and fifth weeks of radiation therapy (50.4 Gy) (n = 14). Oral doxifluridine (700 mg/m^2/day) and leucovorin (20 mg/m^2) were given daily during radiation treatment (n = 14). Quality of life was scored according to 22 activity items (good, >77; fair, >58; poor, <57). Surgical resection was performed 4 weeks after completion of concurrent chemoradiation treatment. Tumor response was classified into CR (complete remission), PR (partial response; 50% diminution of tumor volume or downstaging) and NR (no response).

Results: Tumor response was CR 3/14 (21.4%), PR 7/14 (50%) and NR 4/14 (28.6%) in the IV arm versus CR 2/14 (14.2%), PR 6/14 (42.9%) and NR 6/14 (42.9%) in the Oral arm (p = 0.16, 0.23, 0.24), respectively. The quality of life was poor (36.4% versus 33.3%), fair and good (63.6% versus 66.7%) between the IV arm and Oral arm, respectively. Gastrointestinal toxicity was 2/14 (14.3%) in the IV arm versus 5/14 (35.7%) in the Oral arm, respectively. Stomatitis was only observed in the IV arm (1/14, 7.1%). Hematological toxicity was 3/14 (21.4%) in the IV arm versus 4/14 (28.5%) in the Oral arm, respectively. Systemic recurrence during the follow-up periods were 1/14 (7.1%) in the IV arm and 2/14 (14.3%) in the Oral arm, respectively (p = 0.307). One local recurrence was observed in the Oral arm.

Conclusion: Even though the results were not entirely reliable owing to the small number of patients enrolled, oral doxifluridine-based chemotherapy as preoperative chemoradiation for advanced rectal cancer did not show any significant advantages over intravenous infusion.

Key words: rectal cancer – preoperative chemoradiation – intravenous 5-fluorouracil – oral doxifluridine

INTRODUCTION

Locally advanced rectal cancer, fixed to the rectal wall or surrounding pelvic structures, remains a surgical challenge because it seems to be in an unresectable state or difficult for curative resection. Preoperative chemoradiation treatment has been known to be effective for increasing resectability and decreasing the rate of local recurrences. In several reported series, 70–80% of unresectable lesions can be converted into a resectable state by preoperative combined chemoradiation (1–5). Most of these have used 5-fluorouracil and leucovorin because of the documented benefits of the regimen for colon cancer in both adjuvant treatment and metastatic disease. The

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increase in surgical resectability has been associated with a decrease in local recurrence rates in a several studies (1,2,6). Accurate selection of patients with locally advanced rectal cancer is essential for the prevention of over-treatment. Digital rectal examination and transrectal ultrasonographic evaluation can provide important information with acceptable accuracy rates (7,8).

In general, chemotherapy is often limited by its toxicity and poor patient compliance. Therefore, several clinical trials reported that intrarectal 5-FU administration via suppository minimizes its toxicity and is more effective than intravenous administration (6,9–11)

Recently, oral 5-FU and fluoropyrimidines have been studied and are attracting interest as a means to provide convenience, less toxic treatment and a high quality of life without compromising the treatment efficacy. The rationale for oral 5-FU-based chemotherapy has been known to be able to gain prolonged plasma levels, which can expose the tumor to the drug during concurrent chemoradiation treatment (12,13). Its clinical benefits (e.g. increased quality of life, decreased side effects) have been emphasized. One of the advantages of oral doxifluridine is that it can provide a prolonged 5-FU exposure at a lower peak concentration than those observed with bolus intravenous administration, which mimic the pharmacokinetics of continuous infusion of 5-FU. Theoretically, an oral 5-FU regimen may be more effective in tumor response and result in a higher quality of life. The aim of this prospective randomized trial was to compare the tumor response (therapeutic efficacy), toxicity, quality of life and the rate of recurrence between a standard 5-FU regimen and oral doxifluridine as a preoperative chemoradiation treatment in patients with locally advanced rectal cancer.

MATERIALS AND METHODS

A total of 28 patients with advanced rectal cancer were entered into prospective consecutive trials between July 1997 and December 1998 at the Department of Surgery, Yonsei University College of Medicine. Eligible patients were those over T3N1 or T4, staged with transrectal ultrasonography and or pelvic MRI. The inclusion criteria were Karnofsky performance >90%, age <70 years and provision of informed written consent. Patients were randomly allocated into each treatment arm and compared between the two arms in terms of tumor response (therapeutic efficacy), toxicity, quality of life and rate of recurrence. Randomization lists were stratified by a medical statistician, using randomly permuted blocks of varying sizes. The regimen of the IV arm consist of 5-FU (450 mg/m^2/day) and leucovorin (20 mg/m^2/day) intravenous bolus infusion for five consecutive days during the first and fifth weeks of concurrent radiation treatment (5040 cGy). Doxifluridine (700 mg/m^2/day) was orally administered continuously with oral leucovorin (20 mg/m^2/day) during radiation treatment. None of the patients in either group was hospitalized during preoperative chemoradiation therapy.

Surgical resection was usually performed 4 or 6 weeks following completion of chemoradiation because this interval is recommended for maximum tumor downstaging and the recovery of normal tissues. Preoperative chemoradiation treatment consisted of high-energy photon radiation using a linear accelerator. Patients were treated with a three-field plan (posteroanterior and two lateral wedge field). The top of the field was placed at the L4–5 junction, lateral borders 1–2 cm outside the bony pelvis and inferior margin 5 cm below the tumor. A total dose of 5040 cGy was delivered at 180 cGy/day for 5 days per week for six consecutive weeks. Tumor response was determined from the examination of the surgical specimen. Complete response (CR) meant that no residual microscopic disease or radiation fibrosis replaced the neoplasm. Partial response (PR) meant a downstaging by achieving a >50% diminution of the tumor volume, most of which displayed a total elimination of the exophytic tumor, leaving a flat, firm, irregular mass with a central punched-out ulcer. Toxicity was evaluated by WHO criteria and quality of life was evaluated by a regular check of a questionnaire at the time of out patient department visits during and after chemoradiation treatment. The questionnaire was prepared for checking a total of 22 items of daily activity and scored from 1 to 5 for each item (14) and a research assistant checked the toxicity and reconfirmed the quality of life score by asking about items of daily activities. The calculated score was categorized as poor (<57), fair (58–76) and good (≥77). Following discharge, all patients were regularly followed up at the out patient department whether a local or systemic recurrence had occurred or not. A chi-squared test was used to explore the differences between each group.

RESULTS

There was no difference in gender ratio between the two groups of arms (IV arm, male/female ratio 9/5; Oral arm, male/female ratio 8/6). The mean age of the patients was 50.2 and 57.2 years, respectively. The type of surgery in the IV arm was abdominoperineal resection in five, low anterior resection in seven, Hartmann in one and coloanal anastomosis in one. The type of surgery in the Oral arm showed a similar distribution, abdominoperineal resection in four, low anterior resection in nine and coloanal anastomosis in one (Table 1). CR was present in three of 14 patients (21.4%) in the IV arm and two of 14 patients (14.2%) in the Oral arm ($p = 0.168$). Preoperative staged T3 was downstaged into T0 in two in the IV arm, one in the Oral arm, respectively. Preoperative staged T4 was downstaged into T0 in one in the IV arm and one in the Oral arm. PR was present in seven of 14 (50%) in the IV arm and six of 14 patients (42.9%) in the Oral arm ($p = 0.235$), respectively. No response was present in four (28.9%) of 14 patients in the IV arm and six (42.9%) of 14 patients in the Oral arm, respectively ($p = 0.247$) (Table 2). The overall tumor response rate was present in 10 (71.4%) of 14 patients in the IV arm and eight (51.7%) of 14 patients in the Oral arm, respectively.

Table 1. Patients' characteristics

	IV arm (n = 14)	Oral arm (n = 14)
Gender:		
Male	9	8
Female	5	6
Mean age (years)	50.2	57.2
Type of operation:		
APR	5	4
LAR	7	9
Hartmann	1	0
CAA	1	1

APR, abdominoperineal resection; LAR, low anterior resection; CAA, coloanal anastomosis.

Table 2. Tumor response

Tumor response	IV arm (n = 14)	Oral arm (n = 14)
No response*	4 (28.6%)	6 (42.9%)
Partial response†	7 (50%)	6 (42.9%)
Complete response‡	3 (21.4%)	2 (14.2%)

*p = 0.247. †p = 0.235. ‡p = 0.168.
Partial response: 50% diminution of tumor volume or downstaging; complete response, no microscopic evidence of tumor.

Table 3. Quality of life score

Quality of life score	IV arm (n = 11)	Oral arm (n = 12)
Poor	4	4
Fair and good	7	8

Poor: 4/11 (36.4%) versus 4/12 (33.3%). Fair and good: 7/11 (63.6%) versus 8/12 (66.7%).

The quality of life score was assessed in 11 patients in the IV arm and 12 patients in the Oral arm. A poor score was present in four of 11 (36.4%) in the IV arm versus four of 12 patients (33.3%) in the Oral arm, respectively. Fair and good scores were recorded in seven (83.6%) of 11 patients in the IV arm versus eight of 12 (66.7%) in the Oral arm, respectively. There was no difference in quality of life score between the IV arm and the Oral arm (Table 3). All patients completed the scheduled 5-FU-based regimen at the prescribed dose, so compliance with oral doxifluridine or IV 5-FU was acceptable. Hematological toxicity (leukopenia grade I and II) was present in two (14.3%) of 14 and three (21.4%) of 14 patients, respectively. Grade III leukopenia was present in one patient in the IV arm and one patient in the Oral arm, respectively. Gastrointestinal toxicity (diarrhea grade I and II) was present in two of 14 patients in the IV arm and five of 14 patients in the Oral arm, respectively. Stomatitis grade I was present in one of 14 patients in the IV arm and none of 14 patients in the Oral arm, respectively (Table 4). All patients were available for follow-up. The mean follow-up period was 15 months (range, 6–26 months). Local failure occurred in one (7.1%) of 14 patients in the Oral arm. Systemic failure occurred in one (7.1%) of 14 in the IV arm and two of 14 (14.3%) in the Oral arm (p = 0.307) (Table 5). All three cases of systemic recurrence were liver metastasis.

Table 4. Toxicity profiles

	IV arm (n = 14)	Oral arm (n =14)
Leukopenia		
Grade I and II	2 (14.3%)	3 (21.4%)
Grade III	1 (7.1%)	1 (7.1%)
Diarrhea		
Grade I and II	2 (14.3%)	5 (35.7%)
Stomatitis	1 (7.1%)	0

Table 5. Rate of recurrences

Recurrence	IV arm (n = 14)	Oral arm (n = 14)
Local	0	1 (7.1%)
Systemic	1 (7.1%)	2 (14.3%)*

*p = 0.307.
Mean follow-up period: 15 months (range 6–26 months).

DISCUSSION

Preoperative chemoradiation treatment reduced both the rate of extrapelvic metastases and local pelvic recurrence. Concomitant chemotherapy during radiation treatment has been known to be effective in synergistic tumor cell killing and preventing systemic metastases (1–3,15). Preoperative concurrent chemoradiation treatment for locally advanced rectal cancer reduces tumor volume and can eliminate viable tumor cells at the surgical margin. Overall tumor response has been reported ranging from 60 to 70% and the complete pathological response was from 17 to 29% (1–5). Even though standard intravenous 5-FU administration was used in most medical centers, it is sometimes limited by its toxicity and poor patient compliance. In order to reduce systemic toxicity, suppository delivery of the chemotherapeutic agent is known to be less toxic than intravenous delivery. Suppository administration allows for direct mucosal contact of the cytotoxic drug, increased rectal tissue drug levels and minimized systemic toxicity (6,9).

Takahashi et al. (10) first reported using 5-FU suppositories preoperatively in rectal cancer patients followed by 5-FU suppositories combined with preoperative radiation.

Galandiuk et al. (8) also reported suppository delivery of 5-fluorouracil with less toxicity and a higher rectal tissue con-

centration than intravenous administration. Pokorny et al. (7) reported that 5-fluorouracil and mitomycin C suppository delivery combined with radiation causes less systemic cytotoxicity and is more effective than intravenous administration in animal experiments. Saito et al. (11) reported that preoperative therapy using radiation (42.6 Gy) and 5-FU (750 mg) by intrarectal administration led to an effective tumoricidal effect without any serious complications. If other alternatives to provide chemotherapeutic agents are effective, it may be chosen for its convenience and lower toxicity. Recently, oral 5-FU and fluoropyrimidines have gained interest as a means to provide a convenient, less toxic treatment and a higher quality of life without compromising treatment efficacy. The clinical benefits (e.g. increased quality of life, decreased side effects) have been emphasized. Doxifluridine (5′-deoxy-5-fluorouridine, dFUR) is a synthetic 5-deoxynucleoside derivative that has been shown to have a therapeutic index that is 10–15 times greater than that of 5-FU (16). The biotransformation to FU occurs enzymatically by means of the action of pyrimidine phosphorylase, which in animal models has been shown to be present in higher concentrations in tumor tissues and therefore has led to higher FU concentration and cytotoxic effects in tumors (16,17). Pharmacological studies showed that an oral regimen of doxifluridine can sustain plasma FU levels for a longer period than the intravenous infusion of FU (17). Another important issue in preoperative chemoradiation is a diagnostic tool for the appropriate selection of patients. In our series of patients, transrectal ultrasonography was accurately used to stage and select patients for preoperative chemoradiation because transrectal ultrasonography is known to be a reliable tool with a high accuracy rate for selecting patients for preoperative chemoradiation. Our rate of accuracy of transrectal ultrasonography has been reported and compared with the rate of accuracy of pelvic MRI (7,8). As far as tumor response is concerned, there is no difference from the many reported series. Minsky et al. (1) reported 9% complete pathological response and 91% resectability. Chari et al. (5) reported 27% complete pathological response and 49% tumor response. Even though the regimens of chemotherapy varied, 60–70% tumor response and a high rate of resectability have been reported in many series. In our series, 71% (10 of 14) tumor response in the IV arm and 51.7% (eight of 14) tumor response in the Oral arm were recorded, respectively. Additionally, there was no statistical difference between the IV and Oral arms of treatment in terms of tumor response.

Our data appear to be comparable to the results reported in many other studies of preoperative chemoradiation treatment (1–5,15). In the present series, the rate of complete pathological response also shows no difference between the two arms (21.4%, 3/14 versus 14.2%, 2/14). The effectiveness of oral doxifluridine has been studied as a postoperative adjuvant treatment, resulting in a comparable therapeutic effect, good patient compliance and good quality of life with less toxic effects (12,13,17–19). Previous reports with 5-FU suppository chemotherapy in the setting of the preoperative chemoradiation show a comparable tumor response and lower toxic effects. However, there have been no clinical trials concerning the therapeutic effectiveness and quality of life between conventional intravenous 5-FU and oral 5-FU regimens in the setting of preoperative chemoradiation. As far as toxicity is concerned, the symptoms of toxicity associated with 5-FU-based chemotherapy include leukopenia, diarrhea and stomatitis. Minsky et al. (1) reported that there was grade 3/4 hematological toxicity among patients given 5-FU/leucovorin during preoperative chemoradiation. Chen et al. (2) found that there was no grade 4 toxicity, although grade 3 toxicity was observed (stomatitis in 6% and diarrhea in 13%). They also reported that grade 3 myelosuppression was leukopenia in 3% and anemia requiring transfusion in 6%.

In our series, grade 3 leukopenia was observed in one patient in the IV and Oral arm, respectively. Grade 1 and 2 leukopenia was noted in five of 28 (18%), although there was no difference between the IV arm and Oral arm. Grade I and II diarrhea was more common in the Oral arm (14.3 versus 35.7%). The quality of life score also showed no significant difference between the IV and Oral arms. The main influencing factor affecting the quality of life score during chemoradiation treatment seems to be radiation treatment itself. As far as toxicity profiles and quality of life score are concerned, there is no difference between the IV arm and the Oral arm. However, oral doxifluridine-based chemotherapy regimen as a preoperative chemoradiation shows comparable tumor response and oncological results. Based upon this study, the oral doxifluridine regimen did not show any greater tumor response or higher quality of life than the intravenous 5-FU regimen. As far as oncological safety was concerned, a longer follow-up period was needed. In conclusion, although the number of patients enrolled in each arm of this study was limited, the oral doxifluridine regimen did not show any significant advantages over preoperative concurrent chemoradiation.

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