Int. J. Hyperthermia, August 2006; 22(5): 399–406

informa
healthcare

The synchronization of chemotherapy to circadian rhythms and irradiation in pre-operative chemoradiation therapy with hyperthermia for local advanced rectal cancer

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(Received 31 January 2006; revised 6 April 2006; accepted 2 May 2006)

Abstract

Purpose: The therapeutic and adverse effects of pre-operative chrono-chemoradiation with local hyperthermia for patients with rectal adenocarcinoma were evaluated.

Materials and methods: Pre-operative radiation therapy of a total dose of 40 Gy ($n=10$) or 50 Gy ($n=19$) on the whole pelvis and hyperthermia once a week during the radiation therapy for 1 h were performed for patients with T2–T4 rectal adenocarcinoma. Chemotherapy consisted of 5-FU (250 mg m^{-2} per day) and LV (25 mg m^{-2} per day) administered by continuous infusion in the night for 5 days a week in the second and fourth weeks of radiation.

Results: Grade 3+ toxicities were seen only in two patients (6.9%). A significant down staging was seen in 41.4% of all cases and 52.6% of cases with a radiation dose of 50 Gy. Of the patients who had received surgical resection of a tumour, three (11.1%) had no residue pathologically in the specimen and eight (29.6%) had microscopic lesions.

Conclusions: These results yielded a high response rate with minimal toxicities for advanced low-rectal adenocarcinoma. The administration of 5-FU during the sleeping time before irradiation might have an advantage not only as a chronotherapy but also as a radiation sensitizer.

Keywords: *Chemoradiation therapy, circadian rhythms, hyperthermia, rectal cancer*

Abbreviations: 5-FU, 5-fluorouracil; LV, Leucovorin; APR, abdomino-perineal resection

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ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.1080/02656730600799873

Introduction

Rectal cancer in the lower part of the rectum has a high rate of local recurrence with poor prognosis and the quality of life after radical surgical procedures such as lateral node dissection, which have a limited survival rate, is severely diminished [1]. Since a US National Institute of Health Consensus Conference receiving the results of the Gastrointestinal Tumour Study Group 71–75 trial, pre-operative or post-operative radiation therapy with or without chemotherapy has become the standard procedure for resectable locally advanced adenocarcinoma of the rectum [2].

A large randomized control study indicated that pre-operative chemoradiation was superior to post-operative chemoradiation in local control and toxicity [3], although there was no difference in disease-free and overall survival. Although controversial, chemoradiation therapy increases the use of sphincter-preserving surgery in low-rectal carcinoma patients and contributes to their disease-free and overall survival [4].

In the pre-operative chemoradiation therapy, the concomitant use of 5-fluorouracil (5-FU) based chemotherapy with pelvic radiation is common and a constant infusion schedule is considered to be more beneficial than bolus infusion [5]. However, the doses of chemoradiation therapy and regime of administration are different in many reports and are under investigation. In a recent report, the incidence of an acute Grade 3–4 toxic effect of these therapies was reported to be as high as 27% in patients undergoing pre-operative chemoradiation, although it was less than 40% in patients in post-operative care [3]. Most of the adverse effects were haematological depression, diarrhoea and nausea, which are the major dose-limiting toxicities of 5-FU. Therefore, a specific modulation of pre-operative concomitant therapy with radiation is desired in which the adverse effects are minimized and the effect of radiation is fully enhanced as a radiation sensitizer.

Chrono-chemotherapy is an attractive therapy in which anti-cancer drugs are administered with optimal timing according to the circadian rhythms of anti-cancer action and adverse effects on normal cells [6]. Previously, Levi et al. [7] had reported that chronotherapy with l-OHP +5-FU+Leucovorin (LV) for rectal cancer patients with unresectable liver metastasis made it possible to increase the drug dose intensity and achieve a response rate in excess of 50% in phase II–III studies.

Additional modalities to pre-operative radiation therapy to increase the rate of complete remission were reported. A previous study reported the additional effect of hyperthermia to pre-operative radiation alone without any increase in adverse effects [8]. Local hyperthermic therapy in combination with irradiation has been shown to be less invasive; therefore, the use of local hyperthermia with irradiation for local advanced rectal cancer has potential as a pre-operative therapy because the severe adverse effects of pre-operative therapy should be avoided to decrease perisurgical complications.

In the present study, a concomitant chemotherapy of 5-FU and LV with radiation hyperthermia was started at 9 pm and finished the next morning prior to irradiation therapy expecting the effects as the chrono-modulation and radiation sensitization of 5-FU. The therapeutic and adverse effects of chronochemotherapy and local hyperthermia combined with pre-operative radiation therapy for locally advanced low-rectal adenocarcinoma were evaluated and compared with the results of pre-operative chemoradiation therapy reported previously.

Materials and methods

Twenty-eight patients without distant metastasis were enrolled in the study. Patients with a T2 or T3 rectal adenocarcinoma located in the lower rectum, as well as those with T4 rectal

cancer in the middle or upper part of the rectum, were included in the study (Table I). The protocol was approved by an institutional review board and committee of Gunma University Hospital. Informed consent was obtained from each patient. All of the patients underwent a colonoscopy with a biopsy of the tumour, an ultra-sonography using a miniature probe, a computed tomography (CT) scan and MR imaging of pelvis. Tumour staging was evaluated by surgical oncologists and radiation oncologists. All patients had a performance status of PS 0–1. The same examination was performed to evaluate the therapeutic effect of chrono-chemoradiation therapy with hyperthermia on the primary lesion before surgery. The lymph node status was not included in the criteria for the estimation of down staging.

The radiation treatments consisted of 20 fractions of 2.0 Gy, delivered 5 days a week with a Lineac of 15 MV for a total dose of 40 Gy on the entire pelvis in 10 patients. Intermittent analyses of the initial 11 patients led to a dosage escalation to a total dose of 50 Gy, 25 fractions of 2.0 Gy, for 5 weeks in 19 patients.

In this series, the patients received three sessions of hyperthermia once weekly. Hyperthermia was performed immediately after the irradiation fraction with radiofrequency devices (Thermotron-RF 8, Yamamoto Vinita Co., Ltd., Japan). The applicator with a 30-cm diameter was usually attached to the patient with plastic bags filled with deionized water. For intra-rectal temperature monitoring, a fine plastic tube containing a thermo-couple thermometer was inserted into the rectal cavity close to the tumour. Multiple locations were monitored with a single needle containing a multi-sensor probe. For each monitored location, temperatures were recorded every minute during hyperthermic treatment. Active skin cooling at 5°C was applied to most patients during the treatment. The treatment was conducted while monitoring the vital signs at least every 10 min. Power outputs were increased to the patients' tolerance levels. The aim was to continue treatment for 60 min. Maximum temperatures were taken at the end of each hyperthermic session.

Table I. Patients characteristics.

Characteristics	No. of cases	%	Range
Total no	29		
Male	21	72.4	
Female	8	27.6	
Age	61.2 ± 11.7		37–83
T			
2	3	10.3	
3	24	82.8	
4	2	6.9	
N			
0	10	34.5	
1	6	20.7	
2	13	44.8	
Surgical technique			
APR	7	24.1	
LAR	17	58.6	
Local resection	3	10.3	
None	2	6.9	
Sphincter preserving rate		72.4	
Radiation dosage			
40 Gy	10	34.5	
50 Gy	19	65.5	

Chemotherapy consisted of 5-FU (250 mg m^{-2} per day) and LV (25 mg m^{-2} per day) administered by continuous infusion in the night from 9 pm to 9 am for 5 days (Sunday night to Friday morning) in the second and fourth weeks of radiation for all patients. A CV catheter was used for infusion and the infusion line was removed after heparinization of the CV catheter in the daytime. After an interval of ~8 weeks from the prescribed therapy [9], all patients underwent surgery except two who had a complete response clinically and refused the operation. The patients who refused the operation were followed up intensively with a digital examination, repeated biopsy and MRI study for local evaluation and CT scan for the diagnosis of distant metastasis.

When the tumour was resectable with a margin of normal tissue around the tumour site, the anastomosis was stapled with a circular stapler and ileostomies were diverted. Frozen-section analysis of tissue from the distal margin was used in patients who had a tumour near the distal margin. If the tumour was present at the link margin, patients had an abdomino-perineal resection of the rectum (APR).

Because a partial response to pre-operative chemoradiation was not acceptable, a complete clinical response was chosen as a measure of objective tumour response before resection, defined as an undetectable tumour in MRI/CT/colonoscopy and a negative result of biopsy examination. According to a report by Crane et al. [4], the pathological response was evaluated as cases with either no residual or only microscopic residual disease in the resected specimen. Acute toxicities were scored according to the NCI-CTC ver2.0.

Results

For a total of 87 sessions of hyperthermia, the average value for the maximum temperature ± standard deviation in the rectal cavity was 40.3 ± 0.89°C (range 38.6–41.9).

All patients except one (anorexia) tolerated the chemoradiation therapy with hyperthermia. The toxicities included diarrhoea (one patient in Grade 2 and one in Grade 3) and anorexia (one patient in Grade 3) as gastrointestinal toxicities. No haematological toxicity was observed. Other adverse effects included the following: Grade 1 peri-anal dermatitis due to irradiation in two patients and mild liver damage in one patient in Grade 1. As a whole, only two cases (6.9%) showed toxicity over Grade 3 (Table II). Major perioperative morbidity occurred in two patients (6.9%) and included perineal wound abscess after APR and small bowel obstruction. No other serious complications, such as anastomotic leakage, intra-abdominal abscess or operative death, occurred. No further increase in the adverse effects was observed in the 50 Gy group than in the 40 Gy group.

Table II. Pre-operative complication.

	40 Gy (%)			50 Gy (%)			Total (%)
	Grade 1	Grade 2	Grade 3+	Grade 1	Grade 2	Grade 3+	Grade 3+
Diarrhoea	2	1	1	3	0	0	1
Anorexia	1	0	0	0	0	1	1
Mucositis	0	0	0	1	0	0	0
Haematological	0	0	0	0	0	0	0
Perianal dermatitis	0	0	0	0	2	0	0
Liver dysfunction	1	0	0	0	0	0	0
Total	4 (40.0)	1 (10.0)	1 (10.0)	4 (21.0)	2 (10.5)	1 (3.7)	2 (6.9)

Significant down-staging estimated in the primary lesion, in which tumours were undetectable by MRI and colonoscopy and negative results were obtained from biopsies, was seen in 41.4% of all cases and 52.6% of cases with radiation doses of 50 Gy. APR was performed in the seven patients (24.1%) and sphincter-preserving operations were performed on 20 patients. Local resection from a trans-anal approach was performed in three patients who had a clinically complete response to the pre-operative chemoradiation therapy with hyperthermia. Two patients refused the operation and were followed up for the local and distant recurrence of the tumour. Low anterior resection could be performed in 17 cases (Table I). The sphincter preservation was achieved in 22 patients (72.4%).

The pathological diagnosis obtained from a surgical specimen is shown in Table III. Of patients who underwent surgical resection of a tumour, three (11.1%) had no residue in the specimen and eight (29.6%) had a microscopic lesion (less than 5 mm). The rate of clinical CR was 55.5% in patients with a total radiation dose of 50 Gy, which was significantly higher in 40 Gy ($p = 0.04$).

Discussion

The European Organization for Research and Treatment of Cancer (EORTC) Radiation Group has published results of a phase II trial indicating a dose of 5-fluorouracil (5-FU) combined with a low dose of leucovorin (LV) and pelvic irradiation as the optimal treatment of rectal cancer [10]. Two 5-day courses of a constant infusion of 350 mg m^{-2} per day 5-FU and low-dose LV during pre-operative radiation are recommended. Recently, assessment results of acute toxicity and treatment compliance were published and the protocol used in the EORTC did not alter the compliance with pre-operative radiation therapy. In the same report, Grade 2+ toxicities were seen in 54.3% of patients in the group receiving chemoradiation therapy, a higher percentage than that observed in the group receiving pre-operative radiation alone. It is believed that the adverse effects of pre-operative therapy for resectable carcinoma should be minimized as much as possible to decrease perioperative complications and prevent the impairment of the quality of life. For this purpose, the chronotherapy with 5-FU is enticing. The tolerability and efficacy of chemotherapeutic drugs, as well as that of radiation therapy, vary by 50% or more as a function of dosing time in mice or rats [7, 12]. Tampellini et al. [13] reported on the pharmaco-economic benefit resulting from the decrease in toxicity in chronochemotherapy, which was greater than that with the FOLFOX regime in patients with metastatic colorectal cancer. The best chronotherapy schedule can enhance the patients' quality of life through a reduction in the incidence of the toxic effects while achieving at least similar anti-tumour activity; it can also prolong the survival or increase the cure rate with similar tolerance to that of standard

Table III. Response to the chrono-chemoradiation with hyperthermia.

				Pathological response (%)			
Protocol	*n*	Significant down stage	CR	Microscopic	Macroscopic no resection	Clinical rate%*	CR
40 Gy + CH	10	2/10 (20.0%)	1 (11.1)	0 (0)	8 (88.8)	1	11.1%
50 Gy + CH**	19	10/19 (52.6%)	2 (11.1)	8 (44.4)	8 (44.4)	1	5.5%***
Total	29	12/29 (41.4%)	3 (11.1)	8 (29.6)	16 (59.3)	2	40.7%

*Pathological CR or only microscopic disease/resected cases; ***$p = 0.04$ vs. 40 Gy + CH, χ square test.
CH: Chronochemotherapy (2 weeks) and hyperthermia (4 or **5 times).

Table IV. Comparison of response and toxicity with other reports of pre-operative chemoradiation therapy combined with 5FU constant infusion.

Reference	No. patients	RT (Gy)	Chemotherapy ($mg\,m^{-2}$ per day)	Pathological CR rate	Toxicity	
					Grade 3+	Grade2+
[14]	30	45–54	1000	5 days × 2	20%	23%
[15]	117	45	300	5FU ci 5 days × 5	27%	–
[16, 17]	83	37.8	1000	ci 5 FU 4 days	9%	13%
+10 $mg\,m^{-2}$ MMC × 1	40	50.4	1000	5FU ci 4 days × 2	23%	5%
+CDDP 60 $mg\,m^{-2}$ × 2	40	50.4	1000	5FU ci 5 days × 2	20%	17%
+CDDP 60 $mg\,m^{-2}$ × 2						
[4]	238	45	300	5FU ci 5 days × 5	47%*	–
[3]	421	50.4	1000	5FU ci 5 days × 2	8%	27%
[11]	400	45	350	5FU/LV ci 5 days × 2	–	54.3%
Present study	29	40–50	250	5FU/LV in the night,	11.1%	40.7%*
					6.7%	17.2%
5 days × 2 + Hyperthermia						

*No residual disease or only microscopic disease.
RT: radiation therapy; ci: continuous intravenous infusion.

treatment schedules [6]. Indeed, the results of the present study showed a greater reduction in the adverse effects of pre-operative chemoradiation therapy than has been reported in similar studies [3, 4, 11, 14–17] (Table IV).

The regimen containing a continuous infusion of 5-FU has proved to be superior to the commonly used monthly 5-day bolus regimen used a decade ago in terms of its response rate, progression-free survival and toxicity [5]. Therefore, the recent regimen of pre-operative chemoradiation containing a continued infusion of 5-FU as chemotherapy is considered to be effective. However, there is no standard infusion schedule in the concomitant chemotherapy with pre-operative radiation therapy and various infusion schedules have been used for 5-FU infusion as shown in Table IV. The dose-limiting toxicity may change, or the toxicity profile may be altered, as a consequence of the infusion schedule [5]. Fundamentally, an anti-cancer drug administered during the radiation therapy has a role as a radiation sensitizer. It was considered that the schedule for the infusion of 5-FU during radiation should be decided with the objective of enhancing the radiation effects most efficiently. Therefore, 5-FU was administered in 12 h (Sunday evening to Friday morning) before the time of irradiation in the present study. Probably, this schedule provided a high concentration of 5-FU in the cancer tissue at the time of irradiation and resulted in the adaptation of the 5-FU concentration to circadian rhythms because the optimal time to administer 5-FU as a chronotherapy is at night for humans [18]. The administration of 5-FU during sleep before radiation might have an advantage not only as a chronotherapy but also as a radiation sensitizer.

Of patients treated with radiation consisting of a 50 Gy dose combined with chronochemotherapy and hyperthermia, over 50% showed a complete clinical response rate. For three of these cases, a local resection was performed and followed up carefully. Although the duration of observation after resection was as short as 6 months to 2 years, no recurrence was observed. Local resection in patients whose lesion was dismissed by the pre-operative therapy remains controversial. A report of results after local resection of T0

by pre-operative treatment indicated a satisfactory rate of curability with local resection of these lesions [15, 19, 20]. On the other hand, Stryker et al. [14] reported that two of nine patients with residual nodal disease had no identifiable tumour at the primary site. In the cases with complete clinical responses, no lymph node metastasis was seen. It is well known that the change in the size of lymph nodes after radiation therapy cannot be used to estimate the therapeutic effect. This study could not clarify the effect of pre-operative therapy on the metastatic lesion in regional lymph nodes. However, the lymph node status after pre-operative therapy is important when a trans-anal resection is performed on patients with clinical CR. A more detailed analysis and longer observations in a large number of such cases are needed to determine the clinical management of cases with complete clinical responses by pre-operative treatments.

In addition to therapeutic enhancement, fewer adverse effects were expected from chrono-chemotherapy than from conventional concomitant chemotherapy. Severe adverse effects change the post-operative course and result in more surgical complications after chemoradiation therapy, which are generally serious. The adverse effects, including surgical complications in the presented regimen, were minimal, particularly when compared with those from previous reports, which indicates that it would be possible to increase the dose of chrono-chemotherapy in a subsequent study. The results of the present phase II study of pre-operative chrono-chemoradiation therapy with hyperthermia provide a high response rate with minimal toxicities for advanced low-rectal adenocarcinoma. Dose escalation of chemotherapy might be possible and a randomized study is needed to define the advantage of chronotherapy and hyperthermia combined with a pre-operative radiation therapy for rectal adenocarcinoma.

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