RESEARCH COMMUNICATION

Adjuvant Modified FOLFOX-4 in Patients with Stage III Rectum Adenocarcinoma

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Abstract

Purpose: The aim of this study was to investigate efficacy and toxicity of a modified 5-fluorouracil (5-FU), folinic acid, oxaliplatin (mFOLFOX-4) regimen followed by infusional 5-FU concomitant with radiotherapy for curatively resected stage III rectum adenocarcinoma patients. Patients and Methods: Between April 2005 and July 2009, 55 operated stage III rectum cancer patients were evaluated retrospectively. mFOLFOX-4 regimen (oxaliplatin 85 mg/m2 1st day, folinic acid 200 mg/m2 1st day, 5-FU 400 mg/m2 iv bolus 1st day, 5-FU 1600 mg/m2 46 hours continuous infusion) was applied every 2 weeks. After four courses of mFOLFOX-4, 50.4 Gy (1.8 Gy in 28 fractions) radiotherapy with continuous 5-FU 200 mg/m²/day by infusion pump were given. On completion of chemoradiation four more mFOLFOX-4 courses were given. Results: Median age of the patients was 54 years (range 23-73 years). Low anterior resection was performed in 37 (67.3%) and abdominoperineal resection in 16 (29.1%) . Ten (18.2%) patients were at stage IIIA, 24 (43.6%) at stage IIIB and 21 (38.2%) at stage IIIC. Planned chemotherapy cycles were completed in 92.7% of patients. Grades 3-4 toxicity included neutropenia (9.1%), febrile neutropenia (3.6%), anemia (3.6%), diarrhea (21.8%), neuropathy (9.1%), renal toxicity (3.6%), hepatotoxicity (5.5%). Median follow-up time was 30 (9-57) months. Local recurrence and distant metastasis was observed in 3 (5.5%) and 10 (18.2%) patients, respectively. Ten (18.2%) patients died during follow-up. Three years disease free survival and overall survival were 67.5% and 77.3%, respectively. Conclusion: mFOLFOX-4 following chemoradiotherapy with continuous 5- FU infusion is an effective and well tolerated adjuvant treatment for stage III rectal carcinoma patients.

Keywords: Rectal cancer - adjuvant chemoradiotherapy - oxaliplatin - FOLFOX regimen

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Introduction

Cancerous lesions within 12 cm length from anal verge with rigid proctoscopy are defined as rectum cancer (Nelson et al., 2001). About one- third colorectal cancers are observed in the rectum area (Jemal et al., 2008). The clinical presentation and management of rectal cancers are distinct from colon cancer. Although the possibility of development of liver metastasis is the same for colon and rectal cancers, the rate of lung metastasis in rectum cancer is 11.5%, while it is 3.8% in right colon cancer and 3.4% in left sided colon cancer (Faught et al., 1995). Besides the risk of local recurrence in rectum cancer is higher than the risk of local recurrence in colon cancer. This situation is associated with dismal prognosis (Weiser et al., 2005; Wiig et al., 2005). Kapitejin at al reported a subgroup analysis of rectum cancer recurrence risk according to tumor localization. In this study no difference between surgery only and surgery and radiotherapy combination for the treatment of tumors which settle farther than 10.1 cm away from anal verge was shown, however for the tumors closer than 10.1 cm, the addition of radiotherapy to surgery decreases the risk of recurrence (Kapiteijn et al., 2001).

In most of the epidemiologic studies, because the colon and rectum cancers are evaluated together in colorectal cancers group, it is difficult to find epidemiologic and prognostic data that is peculiar to rectum cancer. The colorectal cancers are in the third order to be seen in the frequency of repetition in the world. According to the data of National Cancer Institute, 108070 colon cancers and 40740 new rectum cancers were diagnosed in the United States of America (USA) in 2008. The number of death for both illnesses was explained as 49960 (Libutti et al., 2008).

Because the local recurrence of rectum cancer is more than that of colon cancer and it has a completely worse prognosis, there are some differences in the treatment of rectum cancer. The differences are applied surgical techniques, using of radiotherapy and different chemotherapy protocols. It is known that, in localized rectum cancer, after curative resection the adjuvant chemoradiotherapy increases the survival (NIH consensus conference, 1990; Thomas and Lindblad, 1988). Intergroup 035 study is important in adjuvant treatment of colorectal cancer (Moertel et al., 1990). In this study,

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levamisol and bolus 5-FU combination have been used, and in comparison with the surgery itself, about 41% decrease in relapse ratio, and 33% decrease in general cancer mortality have been observed. With the help of this data, 5-FU based adjuvant chemotherapy for the patients in stage-III colorectal cancer has commonly been accepted all over the world. The study of Intergroup 0089 has shown that, 5-FU and leucovorin regimen (Mayo Clinic and Rosewell Park) are equivalent (Green et al., 2002). MOSAIC study showed that addition of oxaliplatin to 5-FU and leucovorin (LV) has significant effect on 6-year overall survival and 5-year disease free survival (André et al, 2009).

After MOSAIC study, in the stage III colon cancer, the adjuvant FOLFOX-4 regimen has been accepted as a standard application (André et al, 2009). But, information about the adjuvant chemotherapy of operated rectum cancer is limited. The information about this subject is mostly from the results of the patients who have colon cancer.

In this study, we searched the efficacy and tolerability of chemoradiotherapy as adjuvant treatment formed by modified FOLFOX-4 (mFOLFOX-4) chemotherapy and radiotherapy with continuous 5-FU infusion in operated stage III rectum cancer.

Materials and Methods

Fifty-five operated stage III rectum cancer patients between April 2005 and July 2009 were evaluated retrospectively. Patients were staged according to AJCC TNM 2002 classification (Grene , 2002). Every two weeks mFOLFOX-4 protocol has been given to all patients with central port catheter (on the 1st day 85 mg/ m^2 oxaliplatin, folinic acid 200mg/m^2, 5-FU 400 mg/ m^2 intravenous bolus, 5-FU 1600 mg/m^2 for 46 hours infusion). After 4 courses of mFOLFOX-4, 28 fractions to the front part of the rectum, totally 5040 cGY radiotherapy and 5-FU at a dose of 200 mg/ m^2/ day were given with infusion pumps during radiotherapy. After chemoradiotherapy (15 days later) four more courses of mFOLFOX-4 were given again. The adverse events were evaluated according to criteria of Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) (Trotti et al, 2003).

Disease free survival was determined as time up to local recurrence, metastasis, death or last control from surgery and overall survival has been determined as time up to death or last control. Both of them have been calculated by means of months. The patient survival data was updated by April 2010 and was evaluated retrospectively. Statistical analyses have been done by the help of Statistical Package for the Social Sciences (SPSS 13.0) software. A survival analysis was done according to Kaplan- Meier method.

Results

The characteristics of the patients have been summarized in Table 1. Median age of the patiens was 54 (range 23-73) years. The most common symptom before diagnosis was rectal bleeding (91%).The most frequent distance from anal verge that tumor has been seen was 1-5 cm for 15 (27.3%) patients and 6-10 cm for 19 (34.5%) patients. Low anterior resection (LAR) was performed in 37 (67.3%) patients and abdominoperineal resection (APR) was done in 16 (29%) patients. Median number of resected lymph nodes was 17 (2-56). In postoperative staging, 10 (18.2%) patients were in stage III A, 24 (43.6%) patients were in stage III B, and 20 (36.4%) patients were in stage III C.

Fifty-one (92.7%) patients received the planned chemotherapy courses and 54 (98.2%) patients received chemoradiotherapy. During radiotherapy, all patients were given infusional 5-FU. In three patients (5.5%) the chemoradiotherapy stopped because of grade IV diarrhea and radiotherapy was continued in these patients without

Table 1. Characteristics of the Patients

Characteristic		No (%)
Median age (minimal-maximal)		54 (23-73)
Sex	Male	35 (63.6%)
	Female	20 (36.4%)
Symptoms	Rectal hemorrhage	31 (56.4%)
	Pain	2 (3.6%)
	Constipation	3 (5.5%)
	RH + pain	15 (27.3%)
	RH + constipation	4 (7.3%)
Tumor localization according to anal verge	1-5 cm	15 (27.3%)
	5-10 cm	19 (34.5%)
	10-15 cm	7 (12.7%)
	>15 cm	1 (1.8%)
	Unknown	13 (23.8%)
ECOG performance status	0	20 (36.4%)
	1	28 (50.9%)
	2	7 (12.7%)
Surgical procedure	LAR	37 (67.3%)
	APR	16 (29.1%)
Histological differentiation	Well	18 (32.7%)
	Intermediate	24 (43.6%)
	Poor	2 (3.6%)
	Unknown	11 (20.0%)
Tumor status	T1	1 (1.8%)
	T2	7 (12.7%)
	T3	44 (80.0%)
	T4	3 (5.5%)
Nodal status	N1	34 (61.8%)
	N2	21 (38.2%)
TNM stage	III A	10 (18.2%)
	III B	24 (43.6%)
	III C	21 (38.2%)

LAR, low anterior resection; APR, abdominoperineal resection

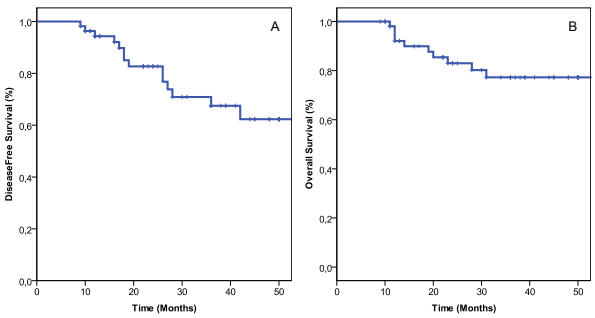

Figure 1. Kaplan-Meier Estimates of Disease-free Survival (A) and Overall Survival (B)

Table 2. Adverse Events Due to Treatment (according to CTCAE v3.0)

Side effects	Grade	
	I / II	III / IV
Leukopenia	14 (25.5%)	5 (9.1%)
Anemia	8 (14.5%)	2 (3.6%)
Thrombocytopenia	0	0
Infection	2 (3.6%)	0
Febrile neutropenia	0	2 (3.6%)
Neuropathy	45 (81.0%)	5 (9.1%)
Renal toxicity	1 (1.8%)	2 (3.6%)
Hepatotoxicity	6 (15.8%)	3 (5.5%)
Diarrhea	14 (25.5%)	12 (21.8%)

5-FU. One (1.8%) patient refused the treatment at the end of the fourth course without taking chemoradiotherapy and three patients with grade IV diarrhea during chemoradiotherapy refused the chemotherapy after radiotherapy. Twenty-nine (52.7%) of the patients received chemoradiotherapy after four courses of mFOLFOX-4 and 25 (45.5%) after two courses of mFOLFOX-4.

Generally, treatment was well tolerated. Most of the adverse events were mild (Table 2). Death due to treatment did not develop in any patient. Granulocyte colony-stimulating factor was not given to any patient. Grade III-IV toxicity was seen as leucopenia in 5 (9%) patients, anemia in 2 (3.6%) patients, febrile neutropenia in 2 (3.6%) patients, renal toxicity in 2 (3.6%) patients, hepatotoxicity in 3 (5.5%) patient, diarrhea in 12 (21.8%) patients and neuropathy in 5 (9.1%) patients. Most of the grade III-IV diarrhea was seen during chemoradiotherapy. Median follow up time was 30 (range: 9-57) months. During this time, 3 (5.5%) patients had local recurrence, 10 (18.2%) patients had distant metastasis, and 10 (18.2%) patients died after recurrence. Rate of disease free survival and overall survival at 3-year was found to be 67.5% and 77.3% (see Figure 1). Gender, histological grade, depth of tumor (T) and N status did not statistically effect the disease free survival. Patients who had APR shorter DFS compared the patients who had LAR (42 vs > 55 months p=0.009).

Discussion

Protection of anal continence and possibility of nerve and organ destruction and additional morbidity are all considered at the time of treatment decision because of the anatomic localization of rectum. In rectal cancer, as the local recurrence is frequent, treatment alternatives targets local recurrence prevention. In rectal cancer local recurrence is related to dismal prognosis (Weiser et al, 2005; Wiig et al., 2005). For this reason, adjuvant or neoadjuvant radiation or chemoradiation are standard approach.

There are limited data on adjuvant chemotherapy in operated rectum cancer and rectal cancer patients are treated according to the data obtained from adjuvant colon cancer studies. Although neoadjuvant radiation or chemoradiation have generally been accepted in Europe and USA for the treatment of stage-III rectum cancer, in our country most of the patients are referred to the medical oncology clinics for adjuvant treatment after having surgical resection (Kapiteijn et al., 2001; Wagman et al., 1998; Saoer et al., 2004; Colorectal Colloborative Group, 2001).

Since the ratio of the local recurrence are very high in stage-III rectum cancer, in this disease group 5-FU based chemotherapy and chemoradiotherapy have been recommended as adjuvant treatment in national and international consensus (NIH consensus conference, 1990; Aykan and Topuz, 2008). Adjuvant chemoradiotherapy regimen has frequently been defined as sandwich application and given before and after the chemotherapy and chemoradiotherapy (Tepper, 2002; Smalley, 2006; O'Connell, 1994). Radiotherapy together with infusional 5-FU application has better effects on longer survival in comparison with bolus application (O'Connell, 1994).

In the present study neutropenia, diarrhea, and neuropathy were the most frequent grade 3 or 4 adverse effects. The main side effect regarding the use of oxaliplatin is peripheral neuropathy. Oxaliplatin induces distal paresthesias during or shortly after the first minutes of infusion. In some cases these neurosensory symptoms increase in intensity with cumulative doses, persist between cycles, and interfere with function (Andre et al., 1999; de Gramont et al., 2000; Extra et al., 1990). In the present study, although 45 (81.1%) of patients had peripheral neuropathy during treatment, most of these episodes were of grade 1. Of the 5 (9.1%) patients who had grade 3 peripheral neuropathy during treatment, grade 3 symptoms were still present in 1 (1.8%) patients at the one-year follow-up visit. Similar findings have been reported among patients with colorectal cancer who were treated with oxaliplatin (André et al., 2009; Cassidy et al., 2006; Bennouna et al., 2007)

In FOLFOX-4 arm of MOSAIC study, it has been observed that 5-year disease free survival was 73.3% and 6-year overall survival was 72.9%, respectively (André et al., 2009). In the present study, in patients with rectum cancer, 3-year disease free and overall survival were 67.5 and 77.3%, respectively.

In the present study, adjuvant mFOLFOX-4 regimen and 5-FU infusion with chemoradiotherapy has been well tolerated by the patients with stage-III rectum cancer and it has been shown that it was an effective treatment option.

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