RESEARCH COMMUNICATION

Evaluation of the Efficacy of Modified De Gramont and Modified FOLFOX4 Regimens for Adjuvant Therapy of Locally Advanced Rectal Cancer

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Abstract

Objective: To evaluate the efficacy of modified De Gramont (mDG) and FOLFOX4 (mFOLFOX4) regimens in patients with locally advanced rectal cancer (LARC). Methods: Patients that received adjuvant chemotherapy (CT) for the treatment of LARC (stage II and III) were retrospectively evaluated. Results: A total of 231 patients were examined. Median age was 58 (range, 18-83) and, of these patients, 36 (15.6%) had stage II and 195 (84.4%) had stage III disease. While the patients with stage II disease received only mDG regimen (36, 100.0%), of the patients with stage III disease, 71 (36.5%) received mDG and 124 (63.5%) received mFOLFOX4 regimen. Patients with stage III disease showed recurrences more often, but this difference was not statistically significant. Similarly, for the patients with stage III disease, there was no statistically significant relation between the adjuvant CT regimen received and the rate of recurrence. In patients with stage II disease, who received mDG, median DFS was 101 months and median OS was 106 months. For the patients with stage III disease, the patients that received mDG showed a median DFS of 78 months and a median OS of 96 months, while the patients that received mFOLFOX4 had a median DFS of 51 months and a median OS of 78 months. Although, for the patients with stage III disease, there are major differences between the two different regimens of CT in terms of DFS and OS, this difference was not statistically significant.When the results were evaluated from the perspective of toxicity, the patients that received mFOLFOX4 showed more toxicity. Neurotoxicity, which was seen in the patients that were given mFOLFOX4, was the most prominent toxicity. Conclusions: mDG and mFOLFOX4 regimens are applicable regimens as adjuvant CT for the treatment of LARC.

Keywords: Locally advanced rectal cancer - adjuvant chemotherapy - Turkey

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Introduction

Colorectal cancer is a common and fatal disease. In USA, annually 148,810 cases are diagnosed, 108,070 of which have colon cancer and the remaining has rectal cancer (Jemal et al., 2008). In both women and men, it is the third most common type of cancer and it is the third leading cause of death. It accounts for 10% of all cancers and 10% for all cancer-related deaths (Libutti et al., 2008). In colorectal cancer, main therapy method is surgery. In colon cancer, post-surgical adjuvant chemotherapy (CT) is recommended for the patients with stage II disease that have some specific risk factors and to all patients with stage III disease. For the patients with stage IV disease, an evaluation is performed on an individual basis and systemic therapies are administered for palliative and, in some patients, for potentially curative purposes (Benjamin, 2008; O'Neil et al., 2008; Libutti et al., 2008).

The treatment for rectal cancer is still one of the unclear subjects of the oncology field, and discussions about other therapies to be added to surgical therapy, which is the main therapeutic modality, are ongoing (Hosein et al., 2008; Libutti et al., 2008). While searching for the methods to be adjunct to surgical therapy, the first studies conducted were to evaluate adjuvant radiotherapy (RT), which was shown to reduce local recurrence rates (Fisher et al., 1988). In the subsequent studies, it was revealed that adjuvant chemoradiotherapy (CRT) was more efficient than adjuvant RT and that this approach prevented local recurrences (Gastrointestinal Tumor Study Group, 1985). and reduced cancer-related deaths (Krook et al., 1991; Wolmark et al., 2000). In the ongoing studies, it was found that neoadjuvant RT, when administered instead of adjuvant RT provided a better control of local recurrences (Gérard et al., 1988), and that neoadjuvant CRT was superior to neoadjuvant RT in preventing local recurrences and trend toward increasing survival (Chari et al., 1995; Sauer et al., 2004; Roh et al., 2009). In our department, the patients with locally advanced rectal cancer are mostly treated using this approach, especially with neoadjuvant

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CRT.

Nowadays, for the adjuvant therapy of stage II and III rectal cancer, infusion of 5-Fluorouracil (5-FU) is commonly used. But the use of adjuvant CT in rectal cancer has been based on the evidence of colon cancer (Takiuchi, 2006). In adjuvant CT of rectal cancer, the role of 5-FU and other agents are still contradictory and, studies of 5-FU or capecitabine plus for other many chemotherapeutic agents – particularly, oxaliplatin, irinotecane – and 5-FU or capecitabine plus for many biological agents, such as bevacizumab and cetuximab are ongoing (Hosein et al., 2008).

As there are more limited number of the studies for adjuvant therapy used in the treatment of rectal cancer than the studies for the treatment of colon cancer in the literature, this study was planned to evaluate the efficacy and the tolerability of adjuvant CT in the treatment of locally advanced rectal cancer (LARC).

Materials and Methods

In this study the files of the patients that received adjuvant CT for the treatment of LARC (stage II and III) and followed-up in Dokuz Eylül University, Faculty of Medicine, Department of Internal Diseases, Division of Medical Oncology between January 1999 – August 2009 were retrospectively evaluated and data about adjuvant CT regimens were collected. After 2003 the majority of patients were admitted. 34 (14.7%) patients were diagnosed between in January 1999-December 2003 and 197 (85.3%) patients in January 2004 - August 2009.

The patients with stage II and III rectal cancer, according to American Joint Committee on Cancer's (AJCC) Cancer Staging 6th edition 2002 TNM staging system (American Joint Committee on Cancer, 2002) were enrolled. Local staging incorporates the assessment of mural wall invasion, circumferential resection margin involvement and lymph nodes status for metastasis. Accordingly, T3-4N0/N+ was considered locally advanced and, T3-4N0 was considered of stage II, as N+ was stage III.

The patients, which were receiving CRT, were given RT 45 Gy at 25 fractions and at a daily dose of 1.8 Gy and, concomitantly, 5-FU 225 mg/m^2/day via a continuous infusion. As adjuvant CT, modified De Gramont (mDG) (Folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as 46-hour infusion given once in every 14 days) or modified FOLFOX4 (mFOLFOX4) (Folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as a 46-hour infusion + Oxaliplatin 85 mg/m^2 given once in every 14 days) regimens were given.

In all patients, pre-operative examinations were performed using thoracic, lower and upper abdominal computerized tomography, lower abdominal (pelvic) magnetic resonance imaging (MRI) and endorectal ultrasound.

The time from the diagnosis to the first recurrence was considered as disease-free survival (DFS) and the time from the diagnosis to the death was considered as overall survival (OS). The performance status of the patients was evaluated according to Karnofsky Performance Status (PS) Scale. In addition, the patients with a PS ≥80 were grouped as "good PS" and the patients with a PS <80 were grouped as "poor PS". The evaluation of toxicity was performed according to World Health Organization Toxicity Grading Criteria.

Table 1. Some Information about the Patients According to the Received Adjuvant Chemotherapy

Characteristics	mDG n (%)	mFOLFOX4 n(%)	p
Stage II	36 (100)	0 (0.0)	
Stage III	71 (36.5)	124 (63.5)	
Pathologic T4 tumor	12 (16.9)	30 (24.1)	
Pathologic T3-4 tumor	45 (63.3)	85 (68.5)	
Pathologic N1 tumor	25 (35.2)	38 (30.6)	
Pathologic N2 tumor	7 (9.8)	22 (17.7)	
Pathologic stage IIIA	9 (12.6)	8 (6.4)	
Pathologic stage IIIB	14 (19.7)	30 (24.1)	
Pathologic stage IIIC	7 (9.8)	22 (17.7)	
12 cures of chemotherapy	80 (74.7)	83 (66.9)	
6 cures of chemotherapy	16 (14.9)	28 (22.5)	
Neoadjuvant CRT received	64 (59.8)	94 (75.8)	0.009
Adjuvant CRT received	27 (25.2)	21 (16.9)	0.121
<60 years-old	49 (45.7)	81 (65.3)	0.001
≥60 years-old	58 (54.3)	43 (34.6)	0.00
>80 Performance	92 (85.9)	118 (95.1)	0.001
>60 Performance	107 (100)	124 (100)	
Perineural Invasion	23 (21.4)	32 (25.8)	0.492
Vascular Invasion	18 (16.8)	21 (16.9)	0.904
Lymphatic Invasion	21 (19.6)	35 (28.2)	0.147
Surgical Margin Positivity	3 (2.8)	18 (14.5)	0.002
Complete Response to CRT	11 (10.2)	10 (8.0)	0.559

mDG, Modified De Gramont; mFOLFOX4, Modified FOLFOX4; CRT, Chemoradiotherapy; performance: According to Karnofsky Performance Status

The statistical analysis of the data was done using Statistical Package for Social Sciences for Windows (SPSS) Version 15.0 software. The mean of two groups was calculated using T test, the independent group ratios were compared using Chi-Square test, DFS and OS were analyzed using Kaplan-Meier method and two survival curves were compared using Log-rank Test. The statistical significance was considered as $p<0.05$.

Results

Patient Characteristics

A total of 231 patients with LARC were retrospectively examined. Median age was 58 (18-83) years. Age and stage characteristics of the patients are given in Table 1. Of the patients with clinical stage II disease, 16 (6.9%) were reported as stage III in the pathologic examination performed after the surgical intervention. Twenty one (9.1%) patients, which showed a complete pathologic response to neoadjuvant CRT, were considered as pathologic stage 0.

As surgical therapy, all patients underwent total mesorectal excision (TME) and, in addition, 158 (68.4%) patients received neoadjuvant CRT and 48 (20.8%) adjuvant CRT. All patients received adjuvant CT. For majority, histopathologic diagnosis was adenocarcinoma.

Therapeutic Regimens

While the patients with stage II disease received only

mDG regimen (36, 100,0%), 71 (36.5%) of the patients with stage III disease received mDG and 124 (63.5%) received mFOLFOX4 regimen. Of the patients with stage III, while old patients with a lower PS more commonly received mDG regimen, the younger patients with a better PS more commonly received mFOLFOX4 regimen. mFOLFOX4 regimen was mostly administered to the patients with both clinical and pathologic stage III disease, majority of whom had pathologic T4 and pathologic N2 tumors. On the other hand, the majority of the patients that received mFOLFOX4 regimen were the with a PS >80 (p=0,001). The patients received adjuvant CT for at least 3 months and median number of cure of CT was 12 (6-12).

Efficacy

85 (36.8%) patients had recurrences and, 21 (9.0%) of them showed only local recurrences, 14 (6.0%) showed local+distant recurrences and 50 (21.6%) showed only distant recurrences. Median time from the diagnosis to the first recurrence was 27.0 months. Data for recurrences are given in Table 3. Ten (27.7%) patients with stage II disease and 75 (38.4%) patients with stage III disease showed recurrences. Although the recurrences were more common in the patients with stage III disease, this difference was not statistically significant (p=0.222). Similarly, among the patients with stage III disease, 27 (38.0%) patients receiving mDG regimen and 48 (38.7%) patients receiving mFOLFOX4 regimen showed recurrence. For the patients with stage III disease, there was no statistically significant relation between the regimen of adjuvant CT received and the rates of recurrence (p=0.925) (Table 3).

For the rates of local or distant recurrence, there was no statistically significant relation between the patients who received mDG or mFOLFOX4 regimen in adjuvant therapy (respectively, p=0.511 and p=0.283). Another important subject, for the rates of local or distant recurrence, there was no statistically significant relation between the received CRT format with regard to the adjuvant or neoadjuvant regimen (respectively, p=0,082 and p=0.021). As a detail, distant organ metastasis in patients received neoadjuvant CRT was found more frequently (p=0.021).

The important prognostic factors in the rectal cancer were examined relationship with recurrences. In multivariate analysis, in the stage III patients, recurrences were found more frequent in patients with positive surgical margins which received mFOLFOX4 and in patients not received both CRT and mFOLFOX4 (respectively, p=0.007 ve p=0.008).

After the neoadjuvant CRT, in twenty one (9.1%) patients to obtain complete pathologic response. In this patients, 11 (52.4%) patients were received mDG and 10 (47.6%) patients mFOLFOX4. Recurrence was detected in 6 (28.6%) patients as three of them had received mDG and three of the mFOLFOX4.

Median duration of follow-up was 40.0 months (range, 8-136 months) and, in entire group, median DFS was 78.0 months and median OS was 96.0 months. In all the patients with Stage II disease, which received mDG, median DFS was 101.0 months and median OS was 106.0 months.

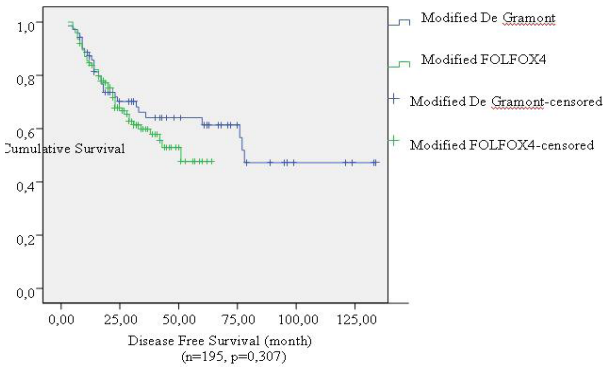

Figure 1. Disease-Free Survival in the Patients with Stage III Disease According to their Regimens of Adjuvant Chemotherapy

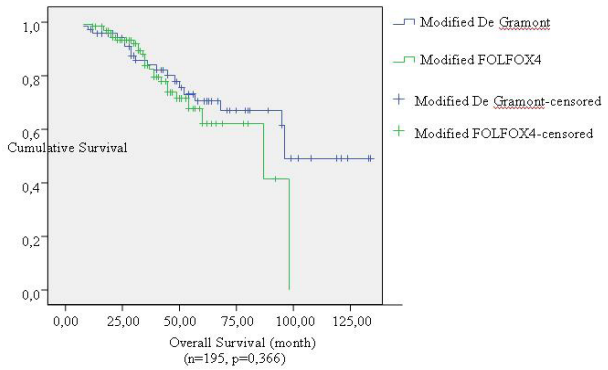

Figure 2. Regimens of Adjuvant Chemotherapy and Overall Survival in the Patients with Stage III Disease

For the patients with Stage III disease, the patients that received mDG showed a median DFS of 78.0 months and a median OS of 96.0 months, while the patients that received mFOLFOX4 showed a median DFS of 51.0 months and a median OS of 78.0 months. Although, for the patients with Stage III disease, two different regimens of CT showed an important difference in terms of DFS and OS, this difference was not found to be statistically significant (respectively, p=0.307 and p=0.366) (Figure 1 and 2).

Toxicity

The toxicities (see Table 2) observed due to adjuvant CT regimens administered were noticeably more common

Table 2. Commonly Seen Toxicities Associated with Adjuvant Chemotherapy

Toxicities	mDG	mFOLFOX4	p
All toxicities	35 (32.7)	82 (66.1)	0.001
Diarrhea	13 (12.1)	18 (14.5)	
Neurotoxicity	1 (0.9)	25 (20.1)	0.001
Mucositis	5 (4.6)	6 (4.8)	
Hand-foot syndrome	5 (4.6)	2 (1.6)	
Hematological	20 (18.6)	56 (45.1)	
Neutropenia	17 (15.8)	48 (38.7)	
Grade ¾ neutropenia	7 (6.5)	22 (17.7)	0.001
Thrombocytopenia	5 (4.6)	24 (19.3)	
Grade ¾ thrombocytopenia	2 (1.8)	11 (8.8)	0.001
Anemia	7 (6.5)	12 (9.6)	
Grade ¾ anemia	3 (2.8)	5 (4.0)	
Neutropenic fever	1 (0.9)	5 (4.0)	

mDG, Modified De Gramont; mFOLFOX4, Modified FOLFOX4

in the patients that were given mFOLFOX4 (p=0.001). The most noticeable toxicity was neurotoxicity, which was seen in the patients that were given mFOLFOX4 (p=0.001). Again, grade ¾ neutropenia and grade ¾ thrombocytopenia were more commonly seen in the patients that were given mFOLFOX4 [for both, p=0.001].

Discussion

Today, while the therapeutic modalities to be used to treat the colon cancer are well-established, the treatment of rectal cancer has not been established yet. It is obvious that the studies for adjuvant CT, which consist a considerable part of the treatment for rectal cancer that requires multimodal approach, are still limited. For this purpose, this study provided the results obtained from the evaluation of adjuvant CT regimens that were administered to the patients with LARC.

In this study, as adjuvant CT, all patients with stage II disease received mDG regimens, while approximately two third of the patients with stage III disease, received mFOLFOX4 and the remaining one third received mDG regimen. The main reasons of giving mDG regimens to these patients, despite their stage III disease, were mostly their advanced age and poor PS. For recurrences, there were no significant differences between stage II and III diseases, and between adjuvant CT regimens in the patients with stage III disease. Although DFS and OS were different between adjuvant CT regimens in the patients with stage III disease, these differences were not statistically significant. While mFOLFOX4 regimen was mostly administered to the patients with both clinical and pathologic stage III disease, majority of whom had pathologic T4 and pathologic N2 tumors, leading to pathologic stage IIIB and IIIC, mDG regimen was mostly administered to the patients with pathologic stage IIIA and IIIB. The rates of toxicity were significantly higher in mFOLFOX4 group.

The studies that reveal the importance of adjuvant CT, another important step of the treatment for rectal cancer, are limited and it is well known that adjuvant CT was generally planned based on the studies conducted for colon cancer. In the majority of the studies that guided this approach, the patients were mostly those with colon cancer, and the patients with rectal cancer were consisting a smaller part of the sample.

The first study for adjuvant CT for the treatment of rectal cancer was done by Fisher et al., which was consisted of three arms: one arm without treatment; one arm with adjuvant RT; and one arm that was given CT composed of 5-FU, semustine and vincristin (MOF). As a result of this study, the arm with adjuvant CT showed significantly prolonged DFS and OS compared to other arms (Fisher et al.,1988). In the study that followed the study of Fisher et al., Wolmark et al. (2000) found that the combination of 5-FU and leucovorine was more efficient than MOF regimen. In this study, the comparison of toxicity performed between two regimens showed the percentages of serious toxicity of 33.0% in the arm of MOF and of 37.0% in the arm of 5-FU plus leucovorine. The most commonly observed toxicities were hematologic toxicity in the arm of MOF and diarrhea in the arm of 5-FU plus leucovorine. In another study that followed the study of Wolmark et al., it was revealed that the rates of recurrence and the rates of death were lower in the patients that were given the combination of 5-FU and folinic acid as adjuvant CT, compared to other patients (Gray et al., 2007). In an important study for adjuvant CT, in which oral therapy was used instead of intravenous therapy in the patients with locally advanced rectal cancer, differently from previous studies, some patients were assigned to the observation arm and the remaining patients were given uracile-tegafur and they were followed-up. In this study, it was found that adjuvant CT prolonged both DFS and OS. Here, mild and moderate toxic effects were 17.0% in CT arm vs. 4.0% in the arm without treatment. The most commonly observed toxicity was reported to be the increase of serum bilirubine levels (Akasu et al., 2006).

Which was shown to be effective in the treatment of metastatic colon cancer, in the adjuvant treatment of colon cancer studies using oxaliplatin plus 5-FU/leucovorin shown to extended survival with the addition of oxaliplatin (André et al., 2004; 2009; Kuebler et al., 2007). However currently, only the use of 5-FU was approved for the treatment of LARC and there is no evidence for the efficacy and the toxicity of the regimens with oxaliplatin. In the studies conducted on the patients with metastatic colorectal cancer, neurotoxicity was the most commonly observed adverse effect with the regimens with oxaliplatin (82%) and this was followed by neutropenia and diarrhea (Fernández-Lobato et al., 2009). Although, for rectal cancer, there are no adequate studies that can modify the existing practice, results of the ongoing studies are being eagerly waited for (Bachet et al., 2010). When we searched the studies about this subject in "clinicaltrials" website, we saw that, as adjuvant CT regimens, the combination regimens with 5-FU, capecitabine, oxaliplatin and irinotecan, and many other biological agents such as bevacizumab and cetuximab added to the drugs cited above were used.

Used in the treatment of rectal cancer, CRT is preventing local recurrences and trend toward increasing survival (Chari et al., 1995; Sauer et al., 2004; Roh et al., 2009) at the same time especially when administered as neoadjuvant, led to better results such as provides complete pathologic response that is very essential for long survival (Lee et al., 2008). Neoadjuvant CRT provided such a benefit and this should not be ignored. In our study, complete response to CRT was found to 9.1% and this rate was acceptable when compared with literature.

The important prognostic factors in the rectal cancer are the presence of a signet ring cell tumor, poor tumor differentiation, tumor localization in the lower regions of the rectum, lymph node involvement, deep tumor invasion, perineural, lymphatic, and vascular invasion, surgical margin positivity, high pre- and post-operative carcinoembryonic antigen level, obesity, and diabetes (Das et al., 2006; Cui et al., 2008; Ianoşi et al., 2008; Libutti et al., 2008). In the presence of poor prognostic factors, administration of CRT and CT in addition to surgery decreased the recurrence rate and prolonged survival (Chari et al., 1995; Sauer et al., 2004; Roh et al., 2009;

Bachet et al., 2010). In this study, patients were examined for poor prognostic factors relationship with received adjuvant CT regimens. In multivariate analysis, in the stage III patients, recurrences were found more frequent in patients with positive surgical margins which received mFOLFOX4 and in patients not received both CRT and mFOLFOX4.

In this study, while mDG regimen was administered to all patients with stage II and to some patients with stage III disease, that had poor performance status and older age, mFOLFOX4 regimen was administered to the patients with stage III disease, who had a good performance status and younger age. The rates of toxicity were significantly higher in the patients that received mFOLFOX4; neurotoxicity, grade ¾ neutropenia and grade ¾ thrombocytopenia were significantly more common in the patients that received mFOLFOX4.

It was observed that, among the patients with stage III disease, the patients that received mDG and the patients that received mFOLFOX4 did not show statistically significant differences in terms of the rates of recurrence and DFS and OS. This could be originated from several reasons. Firstly, the fact that the patients were not randomized due to the retrospective design of the study may be regarded as an important reason. Secondly, while the majority of the patients that received mFOLFOX4 were with both clinical and pathologic stage III disease, the majority of the patients that received mDG were with clinical stage III and pathologic stage II disease. In addition, for the patients with stage III, mFOLFOX4 was mostly given to the patients with pathologic stage IIIB and IIIC disease, and mDG was mostly given to the patients with pathologic stage IIIA and IIIB disease. Although mFOLFOX4 regimen was given to the patients with more advanced stage of tumor in this study, we can conclude that, these patients were similar to other patients in terms of both rates of recurrence and survival values due to higher efficacy of mFOLFOX4 regimen.

We think that the important limiting factors of this study, that we believe to contribute to inadequate data about adjuvant CT in the treatment of LARC, were its retrospective design and, also, the lack of an evaluation of quality of life. Another important matter, for the majority of the patients were diagnosed in 2004 and after, follow-up period was shorter than expected. However, the advantages of this study include the presence of a team experienced in rectal cancer to perform the surgical and medical treatment, the monitorization of these patients and the adequate number of patient enrolled to the study.

Consequently, although there is no currently adequate data about adjuvant CT administered for the treatment of rectal cancer, we can recommend mDG regimen for the patients with stage II disease and mFOLFOX4 regimen for the patients with stage III disease as applicable regimens. However, prospective studies are warranted to elucidate this subject.

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