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# FOLFOX7 regimen in the first-line treatment of metastatic colorectal cancer

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*Doğan Koca[1], Olçun Ümit Ünal[2], İlhan Öztop[2], Uğur Yılmaz[2]*

[1]Department of Medical Oncology, Van Regional Training and Research Hospital, Van, Turkey
[2]Department of Internal Diseases, Medical Oncology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Original Article

## ABSTRACT

**Background/Aims:** We aimed to investigate the efficacy and tolerability of a FOLFOX7 regimen in the first-line treatment of metastatic colorectal cancer (mCRC) patients.

**Materials and Methods:** Patients were evaluated in two groups. Group A did not receive any treatment before, and group B had metastasectomy or metastasectomy plus primary tumor resection.

**Results:** In total, 132 mCRC patients had received FOLFOX7 regimen. The A group consisted of 117 (88.6%) patients, and group B consisted of 15 (11.4%) patients. In the A group, 52.1% had an objective response, 9.4% complete response, 42.7% partial response, 24.8% stable response, and 23.1% progression, and there was a 54.5% rate of primary tumor resection, 22.2% rate of metastasectomy, 80.7% rate of R0 metastasectomy, 19.1% rate of R1 metastasectomy, 15 (10-19) months median progression-free survival, and 32 (22-41) months median overall survival. In the B group, 40 (4-70) months median disease-free survival and 58 (21-94) months median overall survival were found. When toxicities were evaluated, grade 3/4 toxicity was observed in 35.6%. Grade 3/4 hematologic toxicity was the most frequently observed toxicity (29.5%).

**Conclusion:** FOLFOX7 regimen was found to be an efficient and safe regimen for the first-line treatment of mCRC patients.

**Keywords:** Metastatic colorectal cancer (mCRC), first-line chemotherapy, FOLFOX7

## INTRODUCTION

Colorectal cancer (CRC) is a widespread and fatal disease. In the USA, 148,810 new cases are found each year, and 108,070 of these are colon cancer, while the remaining are rectal cancer (1). Colorectal cancer, which constitutes approximately 10% of all cancers, is the third most common malignancy in both genders and is the third leading cause of death. It is responsible of 10% of deaths due to cancer (2). The main method of therapy in colorectal cancers is surgical therapy. Stage I patients are treated only surgically, while a part of stage II patients and stage III patients are given adjuvant chemotherapy (CT) following surgical treatment. In stage IV patients, the main treatment approach is systemic CT, and in some patients, surgical treatment, such as metastasectomy, is also performed (2-4). In rectal cancer, adjuvant or neoadjuvant chemoradiotherapy (CRT) is added in addition to these approaches (5).

Metastatic colorectal cancer (mCRC) constitutes an important part of all colorectal cancers. More than 25% of the patients have metastatic disease at the time of diagnosis. In more than 25% of the remaining patients, metastasis develops during the follow-up period (6). If patients with mCRC are not treated, they have a median survival time of 6 months. However, survival time increases and symptoms related to the disease are controlled with use of CT (7-9). While survival time increases to 12 months with 5-fluorouracil (5-FU) and leucovorin, which are the first-line drugs in treatment, currently, survival time has increased to more than 2 years with new-generation CT drugs, including oxaliplatin and irinotecan, and with addition of targeted drugs, including bevacizumab and cetuximab (10-14). In addition, survival rates have been shown to increase further with current efficient CT, which renders unresectable metastases resectable, and with metastasectomy (15-18).

**Adress for Correspondence:** Doğan Koca, Department of Medical Oncology, Van Regional Training and Research Hospital, Van, Turkey
E-mail: dogankoca@hotmail.com
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In the treatment of mCRC, combination regimens based on 5-FU are still the main therapeutic options. FOLFOX and FOLFIRI regimens, which are constituted by adding oxaliplatin and irinotecan to 5-FU, and combination regimens formed by adding bevacizumab and cetuximab are the most frequently used regimens (19-23). Depending on the dose of oxaliplatin, response rates have been shown to increase in parallel to increasing doses of oxaliplatin, which is contained in FOLFOX regimens performed as different schemes, such as FOLFOX4, FOLFOX6, and FOLFOX7 (24,25).

It is emphasized that CT should be immediately started in patients with mCRC, even if they are asymptomatic (7). On the other hand, in such a case, patients will receive long-term CT, and problems related to long-term side effects of CT and disease progression will occur (26). In addition, all of these may affect surgical morbidity and mortality in patients in whom metastasectomy will be performed. Therefore, an efficient and safe first-line treatment regimen in patients with mCRC is the most critical point.

The FOLFOX7 regimen consists of infusional 5-FU (5-FU; Kocak Farma, Istanbul, Turkey), folinic acid (Leucovorin; Med Ilac, Istanbul, Turkey) and high-dose oxaliplatin (130 mg/m$^2$) (Eloxatin; Sanofi Aventis, Paris, France) (27). The most important problem in this effective regimen is the side effect of oxaliplatin, especially neurotoxicity (28). Therefore, the trend is to use low-dose oxaliplatin-containing regimens. However, such a regimen, which is proven effective, must not be stopped immediately, especially when it is thought to be a combination of monoclonal agents or other new drugs. Also, the first 3 months of treatment of mCRC is important, and FOLFOX7 regimen should be primarily preferred for the first 3 months of treatment of patients with potential resectable or unresectable mCRC. Considering all these issues, data on FOLFOX7 regimen are very important. Thus, we aimed to evaluate the efficacy and tolerability of FOLFOX7 regimen in the first-line treatment of patients with mCRC who had not received CT before.

## MATERIALS AND METHODS

Patients with a diagnosis of mCRC who received FOLFOX7 regimen as the first-line treatment in Dokuz Eylül University, Medical Faculty, Department of Internal Medicine, Division of Medical Oncology between January 2000 and April 2010 were evaluated. The files of the patients were evaluated retrospectively, and data about the efficacy of CT, toxicities, and survival were obtained.

Patients with stage IV colorectal cancer according to the American Joint Committee on Cancer's (AJCC) Cancer Staging 6$^{th}$ edition 2002 TNM grading system who had not received CT before in the metastatic period and who received FOLFOX7 regimen in the metastatic period as the first-line therapy were included in the study (29).

Patients were evaluated in two groups. Group A was chosen from the patients who had not received any treatment including surgery, CT, etc., before, and group B was chosen from the patients who had undergone metastasectomy or metastasectomy plus primary tumor resection and had not received CT.

FOLFOX7 regimen included folinic acid 400 mg/m$^2$ + 5-FU 400 mg/m$^2$ bolus + 5-FU 2400 mg/m$^2$ 46-hour infusion + oxaliplatin 130 mg/m$^2$ every 14 days.

Response was evaluated after every 6 cycles. Evaluation of response was done according to tumor response assessment criteria of the World Health Organization (30). Accordingly, disappearance of the tumor completely was considered a complete response (CR), regression of the target lesion with a rate of 50% or more was considered a partial response (PR), regression of the target lesion less than 50% or progression of the target lesion less than 25% was considered stable disease (SD), and progression of 25% or more in the target lesion or observation of a new lesion was considered progressive disease (PD). The total of CR and PR was evaluated as the objective response rate (ORR).

After 6 cycles CT, a 50% or more reduction in serum carcinoembryonic antigen (CEA) level was considered tumor marker response. Evaluation of toxicity was done according to National Cancer Institute-Common Toxicity Criteria Version 2.0 (31).

Newly diagnosed mCRC patients who had undergone metastasectomy or metastasectomy plus primary tumor resection and who had no radiological finding of disease and after receiving CT from the diagnosis to recurrence was considered disease-free survival (DFS). In mCRC patients with radiological findings of tumor, the time from the beginning of the first cycle day 1 of CT to development of progression was considered progression-free survival (PFS). The time from the diagnosis of metastases to death was considered overall survival (OS).

Statistical analysis of the data was done using Statistical Package for Social Sciences for Windows (SPSS) Version 15.0 software. Kaplan-Meier method was used for analyses of DFS, PFS, and OS. Two survival curves were compared using log-rank test. The statistical significance was considered $p<0.05$.

## RESULTS

### Patient characteristics

A total of 132 patients were evaluated. Group A consisted of 117 (88.6%) patients and group B consisted of 15 (11.4%) patients. The median age of all patients was 59 (18-79); 33 (25.0%) patients were female and 99 (75.0%) were male. Also, 69 (52.3%) patients had metastatic colon cancer, and 63 (47.7%) had metastatic rectal cancer (Table 1).

At the time of diagnosis, 100 (75.8%) patients had no previously diagnosed colorectal cancer or newly diagnosed mCRC,

**Table 1.** General characteristics of the patients

| Characteristic | | n (%) |
|---|---|---|
| Gender | | |
| | Female | 33 (25.0) |
| | Male | 99 (75.0) |
| Primary tumor localization | | |
| | Colon | 69 (52.3) |
| | Right | 17 (12.9) |
| | Middle | 19 (14.4) |
| | Left | 33 (25.0) |
| | Rectum | 63 (47.7) |
| | Upper | 17 (12.9) |
| | Middle | 20 (15.2) |
| | Lower | 26 (19.6) |
| Histopathology | | |
| | Adenocarcinoma | 118 (89.4) |
| | Other | 14 (10.6) |
| Serum CEA | | |
| | 5 ng/mL and higher | 107 (81.0) |
| | Lower than 5 ng/mL | 25 (19.0) |
| Not diagnosed colorectal cancer previously, newly diagnosed metastatic colorectal cancer | | 100 (75.8) |
| Diagnosed colorectal cancer previously, diagnosed metastases in follow-up colorectal cancer process | | 32 (24.2) |
| | Primary colon | 6 (4.5) |
| | Primary rectum | 26 (19.6) |
| | History of adjuvant CT | 25 (18.9) |
| | History of neoadjuvant CRT | 20 (15.1) |
| | History of adjuvant CRT | 3 (2.2) |
| Operated primary tumor before first-line CT | | 55 (41.6) |
| Metastatic organ | | |
| | Liver | 91 (68.9) |
| | Findings indicating intraabdominal tumor invasion | 38 (28.7) |
| | Lung | 35 (26.5) |
| | Bone | 8 (6.0) |
| | Ovary | 2 (1.5) |
| | Supraclavicular lymph node involvement | 2 (1.5) |
| | Spleen | 2 (1.5) |
| | Metastasis in two organs | 32 (24.2) |
| | Metastasis in more than two organs | 8 (6.0) |
| First-line CT received patients | | |
| | Group A patients | 117 (88.6) |
| | Group B patients | 15 (11.4) |
| Second-line CT received patients | | 92 (69.6) |
| Third-line CT received patients | | 41 (31.0) |
| Fourth-line CT received patients | | 20 (15.1) |
| Fifth-line CT received patients | | 5 (3.7) |

CEA: carcinoembryonic antigen; CT: chemotherapy; CRT: chemoradiotherapy; Group A: not receiving any treatment before; Group B: performed metastasectomy or metastasectomy plus primary tumor resection

and 32 (24.2%) patients had colorectal cancer diagnosed and treated previously and newly identified metastases in the follow-up process. Most patients who had diagnosed metastases in the follow-up process had rectal cancer (Table 1).

The most commonly observed metastatic organ was the liver (68.9%); 24.2% of the patients had two-organ metastasis, and 55 (41.6%) of the patients had their primary tumor operated before CT was started (Table 1).

**Table 2.** Efficacy provided by the treatment administered

| Features | Month (range) | % | n (%) |
|---|---|---|---|
| In group A patients | | | 117 (88.6) |
| Median PFS | 15.0 (10-19) | | |
| Median OS | 32.0 (22-41) | | |
| 1 year OS | | 84.1 | |
| 3 years OS | | 44.4 | |
| 5 years OS | | 28.3 | |
| Complete response | | | 11 (9.4) |
| Partial response | | | 50 (42.7) |
| All response rates | | | 61 (52.1) |
| Stable disease | | | 36 (30.7) |
| Progressive disease | | | 35 (29.9) |
| Patients who had undergone primary tumor resection | | | 42 (54.5)* |
| R0 resection | | | 34 (80.9) |
| R1 resection | | | 8 (19.1) |
| Patients who had undergone metastasectomy | | | 26 (22.2) |
| R0 resection | | | 21 (80.7) |
| R1 resection | | | 5 (19.3) |
| Liver metastasectomy | | | 21 (80.7) |
| Peritonectomy | | | 4 (15.4) |
| Lung metastasectomy | | | 2 (7.7) |
| Splenectomy | | | 1 (3.8) |
| Oophorectomy | | | 1 (3.8) |
| Patients whose serum CEA levels decreased | | | 75 (70.1)** |
| Patients whose serum CEA level decreased below 5 ng/mL | | | 12 (11.2)** |
| In group B patients | | | 15 (11.4) |
| Median DFS | 40.0 (4-70) | | |
| Median OS | 58.0 (21-94) | | |
| 1 year OS | | 100.0 | |
| 3 years OS | | 71.1 | |
| 5 years OS | | 35.6 | |
| Recurrence | | | 7 (46.6) |

PFS: progression-free survival; DFS: disease-free survival; OS: overall survival; CEA: carcinoembryonic antigen; Group A: has not received any treatment before; Group B: performed metastasectomy or metastasectomy plus primary tumor resection
*Tumor resection was performed in 42 (54.5%) of 77 patients whose primary tumor was not resected.
**Reduction was observed in 75 (70.1%) of 107 patients whose serum CEA level was high. In 12 (11.2%) of 107 patients, the level decreased below 5 ng/mL.

## Treatment regimens

FOLFOX7 regimen was used in group A and B patients, and the median number of cycles was 6 (4-12). After receiving FOLFOX7 regimen, second-line CT was performed in 92 (69.6%) patients, 41 (31.0%) patients received third-line CT, 20 (15.1%) patients received fourth-line CT, and 5 (3.7%) patients received fifth-line CT (Table 1).

## Efficacy

In group A, ORR was obtained in 61 of 117 (52.1%) patients; 11 (9.4%) of these had CR, and 50 (42.7%) had PR. SD was obtained in 29 (24.8%) patients, and progression was observed in 27 (23.1%) patients (Table 2).

In group A patients, median PFS was found to be 15 months (10-19), median OS was found to be 32 months (22-41), and survival rates at years 1, 3, and 5 were found to be 84.1%, 44.4%, and 28.3%, respectively. In group B patients, median DFS was found to be 40 months (4-70), median OS was found to be 58 months (21-94), and survival rates at years 1, 3, and 5 were found to be 100.0%, 71.1%, and 35.6%, respectively (Table 2).

**Table 3.** Side effects caused by treatment

| Characteristic | Grade 1/2 side effects n (%) | Grade 3/4 side effects n (%) | n (%) |
|---|---|---|---|
| All | 72 (54.5) | 47 (35.6) | |
| All hematological side effects | 67 (50.7) | 39 (29.5) | |
| Anemia | 55 (41.6) | 12 (9.0) | |
| Neutropenia | 26 (19.6) | 28 (21.2) | |
| Thrombocytopenia | 30 (22.7) | 11 (8.3) | |
| Diarrhea | 12 (9.0) | 10 (7.5) | |
| Neurotoxicity | 17 (12.8) | 8 (6.0) | |
| Oral mucositis | 14 (10.6) | 6 (4.5) | |
| Hand foot syndrome | 9 (6.8) | 2 (1.5) | |
| Allergic reaction | 8 (6.0) | 0 (0.0) | |
| Skin eruption | | | 4 (3.0) |
| Neutropenic fever | | | 2 (1.5) |
| Deep vein thrombosis | | | 2 (1.5) |

Compared with group A (group B patients received adjuvant CT), OS of patients in group B was found to be significantly longer (p=0.001).

Serum CEA level reduction was observed in 75 (70.1%) patients who had a high level of serum CEA. In 12 (11.2%) patients who had a high serum level of CEA, it decreased to below 5 ng/mL (Table 2).

In group A, primary tumor resection was performed in 42 (54.5%) of the patients, and metastasectomy was performed in 26 (22.2%) of the patients. In 9 of these patients, both primary tumor resection and metastasectomy were performed. Hepatic metastasectomy was most commonly performed. R0 and R1 resection rates in the patients who had undergone primary tumor resection were 80.9% (34 patients) and 19.1% (8 patients), respectively. R0 and R1 resection rates in the patients who had undergone metastasectomy were 80.7% (21 patients) and 19.3% (5 patients), respectively (Table 2).

### Toxicity

Grade 3/4 toxicity was observed in 47 (35.6%) patients. The most commonly observed toxicities included hematologic toxicity (29.5%), diarrhea (7.5%), neurotoxicity (6.0%), and oral mucositis (4.5%). Grade 1/2 neurotoxicity was observed with a rate of 12.8% (Table 3).

When hematologic toxicities were evaluated, the most common hematologic toxicity was found to be neutropenia (21.2%). This was followed by anemia (9.0%) and thrombocytopenia (8.3%). Neutropenic fever was observed with a rate of 1.5% (Table 3).

## DISCUSSION

Colorectal cancer is the third leading cancer among all cancers. Approximately half of colorectal cancers are metastatic at the time of diagnosis or become metastatic and need treatment subsequently. Currently, median survival has increased to more than 2 years due to advances in CT drugs used in recent years. In addition, it was observed that CT alleviated symptoms, prevented tumor progression, and rendered metastasectomy feasible by decreasing the volume of the tumor, even if more than one metastasis was present. Considering that CT should be started immediately in mCRC patients, even if they are asymptomatic, and especially because first-line CT is more beneficial, the importance of the CT regimen used for first-line treatment increases further. For this objective, it was appropriate to give 132 patients FOLFOX7 regimen as the first-line treatment for mCRC who had not received CT previously.

In our study, in group A, 52.1% had an objective response, 9.4% complete response, 42.7% partial response, 24.8% stable response, and 23.1% progression and a 54.5% rate of primary tumor resection, 22.2% rate of metastasectomy, 80.7% rate of R0 metastasectomy, 19.1% rate of R1 metastasectomy, 15 (10-19) months median PFS, and 32 (22-41) months median OS. Survival rates at years 1, 3, and 5 were found to be 84.1%, 44.4%, and 28.3%, respectively. In group B, 40 (4-70) months median DFS and 58 (21-94) months median OS were found. Survival rates at years 1, 3, and 5 were found to be 100.0%, 71.1%, and 35.6%, respectively.

While 5-year survival rates in mCRC patients in the literature are below 1% when the 5-FU/leucovorin combination is used (32), it has reached 9.8% when oxaliplatin, which is a platin group drug inhibiting DNA replication and transcription, is added to this combination (33). After it was found that response rates and survival times were superior compared to IFL (irinotecan, 5-FU bolus, leucovorin) when oxaliplatin was combined with 5-FU, regimens containing higher doses of oxaliplatin were tried, and survival rates exceeding 2 years were obtained with FOLFOX7 regimen used for this objective, and it was suggested that high-dose oxaliplatin was efficacious; further studies, especially investigating combinations with monoclonal antibodies, were recommended (24,25,27,34,35). Subsequently, studies that added monoclonal antibodies to FOLFOX regimen and used bevacizumab and cetuximab as monoclonal antibodies showed that survival times increased significantly with these combinations (22,23).

After oxaliplatin was found to be efficacious in mCRC patients, studies about how oxaliplatin should be given showed that high doses administered intermittently did not affect efficacy negatively, and side effects, including mainly neurotoxicity, were tolerated better (35). While it was emphasized that FOLFOX regimen, which has an efficacy proven by biochemical tests (36), should not be discontinued completely, it was shown that disease control worsened and disease progressed earlier (37).

As another important issue, in the literature, it was demonstrated that metastasectomy, which is an important step in the treatment of mCRC, increased survival in appropriate patients (15-18) and that administration of FOLFOX regimen as neoadjuvant treatment rendered metastasectomy feasible and decreased disease recurrence and progression after metastasectomy (38). In our study, results received from group A patients were consistent with the literature. When comparing the result obtained with FOLFOX7 regimen containing high-dose oxaliplatin with the results of the studies that combined monoclonal antibodies with FOLFOX regimens containing low-dose oxaliplatin (22,23), our results were found to be as successful as the results of those studies.

Considering that it was shown that metastasectomy increased survival in mCRC patients, it is important to determine potential metastasectomy candidates initially and to administer highly efficient CT as neoadjuvant treatment. On the other hand, increase in the time of neoadjuvant CT may increase the risk of perioperative morbidity and mortality related to the metastasectomy process. Due to all these factors, it is beneficial to administer a CT regimen that will be efficient in a short time in potential metastasectomy candidates. In this context, FOLFOX7 regimen possesses the properties to fulfill this requirement with its higher dose of oxaliplatin.

Another advantage of preferring FOLFOX7 regimen in mCRC patients initially is that it provides the possibility to use a regimen containing oxaliplatin again in the future, since neurotoxicity caused by oxaliplatin is reversible (28).

In addition, in our study, in group A, 80 (68.3%) patients in second line and 25 (21.3%) patients in third line received bevacizumab combination treatment. In group B, 7 (46.6%) patients in second line received bevacizumab combination treatment. K-ras mutations were analyzed in 34 patients. Among those patients, 14 (41.1%) were wild-type (12 patients group A, 2 patients group B). In group A, 5 (4.2%) patients in second line and 16 (13.6%) patients in third line received cetuximab combination treatment. In group B, 4 (26.6%) patients in third line received cetuximab combination treatment.

In our study, grade 3/4 toxicity was observed in 35.6% of the patients, and the most commonly observed grade 3/4 toxicities included hematologic toxicity (29.5%), diarrhea (7.5%), neurotoxicity (6.0%), and oral mucositis (4.5%). Grade 1/2 neurotoxicity was observed with a rate of 12.8%. The most commonly observed grade 3/4 hematologic toxicity was neutropenia (21.2%). When these results were compared with the rates of toxicity reported in the literature, we found that similar results were obtained, except for neurotoxicity rates, which were found to be lower in our study (27,34-38). Low-rate neurotoxicity was attributed to the retrospective study.

Since our study was a retrospective study, it has disadvantages related to retrospective studies. However, regarding a subject like treatment of mCRC, which concerns a large number of patients, we thought that it would be beneficial to present a FOLFOX7 regimen that contains a high dose of oxaliplatin in the first-line treatment of patients who had not received CT previously for the treatment of mCRC to the literature, though we used retrospective data.

Consequently, we can state that FOLFOX7 regimen provides a significant survival advantage in treatment-naive mCRC patients, provides reduction in the volume and number of metastatic tumors when administered as neoadjuvant treatment, and thus renders metastasectomy feasible, increases PFS with a significant rate in patients who have not undergone metastasectomy, increases survival parameters when used as adjuvant CT after metastasectomy in patients with resectable metastasis, and has easily manageable side effects. Currently, prospective studies combining monoclonal antibodies with FOLFOX regimen suggest that response rates will increase further with administration of FOLFOX 7 regimen that contains a high dose of oxaliplatin instead of low oxaliplatin doses.

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