# Metastatic Colo-Rectal Cancer, 2005-2008: Treatment results

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## Abstract

**Introduction:** Colo-rectal cancer has 10% prevalence, among all of the cancer proportionally and also it is the third common cancer in the both sexes. Two recently introduced active drugs in the treatment of advanced colorectal cancer (ACC) are irinotecan and oxaliplatin. The combinations of oxaliplatin (OXA) or irinotecan (IRI) with 5FU-LV have been accepted as standard treatment for metastatic colorectal cancer.

**Patients and Methods:** fifty four patients with colo-rectal cancer who came to the Oncology Clinic of Kermanshah University were assessed over a period of 4 years (2005-2008). All cases in stage III were treated by FOLFOX, unlike the patients in Stage IV treated with FOLFOX during 8 cycles fallowed by FOLFIRI in the same cycles (Sequential method).

**Results:** the age average was less (49.1 years versus 55 years) than in other studies (6). A parallel analyzation of solid data, overall survival (OS), progression free survival (PFS) were 18 and 17.3 months, respectively.

**Conclusion:** FOLFOX and FOLFIRI were administrated in 8 cycles each concomitantly (Sequential form) which provided considerable response with manageable complications. The result of the treatment in the study was correlated with other trials utilizing more modern procedures of medication like 'Target therapies' (OS; 18.4m for CT versus 19-20m for target therapies).

**Key words:** Oxalliplatin, Irrinotecan, Colorectal cancer

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## Introduction

Colo-rectal cancer accounts for 10% of all cancer proportionally, and it is the third most common cancer in the both sexes. Annually, 800 thousand new cases of this cancer are diagnosed and, unfortunately, near half of them die per year.(1) this is the second leading cause of cancer deaths in Western countries. Just in the USA, in 1998, 131,000 new cases of colo-rectal cancer were diagnosed, but, totally, 56,500 of those died.(2)

There is a significant variation in the geographical prevalence of this cancer. In some regions of Asia and Latin America this type of canceer is rare but, in North America and Europe, the occurrence of colo-rectal cancer is 40 times greater. For example in the American Indian population of Alaska, the prevalence is 70 cases per 100,000 while in Aljazeera, it is 2 in a population of 100,000. It is clear that, immigration from the region with a low prevalence to a higher one increases the risk of incidence of this cancer. Similar to other malignancies, colo-rectal cancer is multi- factorial. Age, is the most important risk factor, thus, the prevalence of the occurrence of a sporadic form of this cancer is augmented remarkably above 45 years of ages. Clearly, statistics demonstrate that, the rate of this cancer is doubled over each ten year period of life. In addition to age, dysmorphic changes in the lumen epithelium of the colon is also the principal reason for the development of polyp form lesion (particularly adenoma). This is the major predisposing factor for the occurence of colorectal cancer in later years.(3) Besides this, the familial form of this cancer in first or second generation of relatives is a considerable potentiality.(4,5,6) In the sporadic form of colon cancer not only is age, a

**Table- 1. Characteristic of patients**

| | |
|---|---|
| **Mediane Age** | 49 yr(20-70) |
| **Sex:** | |
| **Male** | 31 |
| **Female** | 23 |
| **Location:** | |
| **Colon** | 34 |
| **Rectum** | 20 |
| **Stage:** | |
| **I** | |
| **II** | 17(31.5%) |
| **III** | 19(35.2%) |
| **IV** | 18(33.3%) |
| **Performance status:** | |
| **0** | 65 |
| **1** | 23 |
| **2** | 12 |

main issue, but also, environmental, nutritional, obesity and taking exceed calories, as an important and independence parameters, have direct impact in this cancer.(7,8) Abnormal BMI (Body Mass Index), specifically more than 30, augments the risk of rectal cancer in men. Finally, the role of genetics and many syndromes like Lynch, FAP and HNPCC in This cancer can not be ignored. The treatment of colo-rectal cancer is based on multi- disciplinary modalities.

Surgery, chemotherapy and radiotherapy play their own specific role in the process of treatment. For sure, the metastatic setting needs more advancement as well as, intensive and subtle care to reach a better overall survival rate (OS) and enhancing a noticeably better quality of life (QOL). Two new drugs, irinotecan and oxaliplatin, have demonstrated an improvement of the survival, when given either alone or in combination with LV-FU, in the first- or second-line of therapy.

In this study, the patients' response to sequential chemotherapy (8 cycle FLOFOX 4 followed up by an 8 cycle of FOLFIRI) and its improved effects on the total aspects of their lives were assessed.

## Material and methods:

Fifty four patients with colo-rectal cancer who came to the oncology clinic of Kermanshah University of Medical Sciences were assessed over a period of 4 years (2005-2008).

These patients mainly had come from Kermanshah and surrounding provinces (Kordestan, Lorestan and Hamedan). The eligibility criteria for inclusion in the study were: adenocarcinoma of the colon or rectum, unresectable metastases, adequate bone marrow, renal function (ceratinine> 1.5), WHO performance status (PS) of 0 to 2 and aged 18 to 75 years.

In this study, exclusion criteria included patients with low performance status and ceratinin>1.5. The average age of patients was 49.1 years (20 up to 77 years). 31 of them were male and 23 were female. Rectal cancer was diagnosed in 20 patients and 34 had colon cancer in which 17 (31.5%) was in stage II, 19 (35.2%) in stage III and 18 (33.3%) in stage IV (Table-1).

All of the cases in stage III were treated with FOLFOX, unlike the patients in Stage IV who received FOLFOX 8 cycles fallowed by FOLFIRI during the same cycles (Sequential method). For patients in stage III and IV, two protocols (FOLFOX and FOLFIRI) were established. FOLFOX encompassed Oxaliplatin 85 mg/m² IV infusion in 2 hours on day1, Leucoverin 200 mg/m² IV infusion in 2 hours on day 1 and 2, 5-FU 500 mg/m² on day 1 and 2, bolus, and also 5-FU 600 mg/m² continuous infusion in 21 hours on day 1 and 2.

This regiment was repeated every 2 weeks for 8 cycles. If we were confronted with an unacceptable response, FOLFIRI protocol was administred also for 8 cycles as a complimentary treatment. The details of this regiment are, CPT-11 180 mg/m² IV infusion in 90 minutes on day 1, Leucoverin 200 mg/m² IV infusion in 2 hours on day 1 and 2; 5-FU 500 mg/m² on day 1 and 2, bolus, and also 5-FU 600 mg/m² continuous infusion in 21 hours on day 1 and 2 (completely similar to FOLFOX).

Total assessment of the patients was categorized as medical history, medical and paramedical evaluations which were regularly performed, particularly before starting treatment. Toxicity was assessed before starting each 2-week cycle using the National Cancer Institute-Common Toxicity Criteria.

A specific scale was used for sensory neurotoxicity: Grade 1 is short lasting paresthesia with complete regression before the next cycle; Grade 2 is persistent paresthesia or dysesthesia without functional impairment; Grade 3 is persistent functional impairment. Chemotherapy was delayed until recovery if neutrophils $1.5\times10^9$/L, platelets $100\times10^9$/L, or significant persistent nonhematologic toxicity.

The dose of irinotecan was reduced to 150 mg/m$^2$ for grades 2 to 3 neutropenia, thrombocytopenia, and diarrhea. The doses of oxaliplatin were reduced to 50 mg/m$^2$ for grade 3 neutropenia, grade 3/4 thrombocytopenia, or grade 4 diarrhea. Where the case of grade 2 paresthesia, oxaliplatin was first reduced to 55 mg/m$^2$, and, if the paresthsia

**Table- 2. Side effect and toxicity associated with Oxaliplatin and Irinotecan**

| Oxaliplatin | | Irinithecan | |
|---|---|---|---|
| **Sign/Symptom** | **Incidence** | **Sign/Symptom** | **Incidence** |
| **Peripheral neuropathy** | 20% | **Diarrhea** | Common |
| **Hepatoxicity** | 0% | **Febrile neutropenia** | 6% |
| **Fatigue** | Common | **Nausea** | Common |
| **Neutropenia** | 60% | **Vomiting** | Not common |
| **Nausea** | common | **Fatigue** | common |
| **Vomiting** | uncommon | **Alopecia** | 48% |
| **Diarrhea** | 7% | **Mucocits** | 17% |

**Table- 3. Incidence of common toxicity with the FOLFOX and FOLFORI regimen**

| | **FOLFOX** | **FOLFIRI** |
|---|---|---|
| **Neutropenia** | 60% | 75% |
| **Febrile neutropenia** | 3% | 6% |
| **Laryngial parestesia** | One patient | 0 |
| **Anemia** | - | - |
| **Nause/Vomiting** | - | - |
| **Diarrhea** | 7% | Common (17% grade3/4) |
| **Mucositis** | 7% | 17% |
| **Neurological** | 20% | 3% |
| **Alopesia** | 5% | 48% |
| **Fatigue** | - | - |

persisted, to 40 mg/m$^2$. In cases of persistent painful paresthesia or grade 3 neurotoxicity, oxaliplatin was omitted from the regimen. Physical examinations and blood counts were performed every cycle. Hepatic, renal function tests and computed-tomography (CT) scans of measurable lesions were assessed at baseline and repeated every four cycles. Subsequently, along with CT scan, sonogeraphy and lab tests, response to chemotherapy and tumor status were determined at every 8 week interval.

Lastly, all of the collected data was analyzed by SPSS and also Kaplan-miere to verify the overall survival rate.

## Results

The evaluation of demographical data suggested that, as a comparison to the official results in Western countries, the age of diagnosis was less (49.1 years versus 55 years).(6) In a parallel analyzation of solid data manifested, OS (Overall Survival), PFS (Progression Free Survival) for (stageIV) were 18 and 17.3 months, respectively. 61 percent of people with stage III colon cancer are still alive without metastasis. The prevalence of visceral metastasis was considerably higher in Rectal cancer where 12 cases out of 20 had this form of metastasis (60%).

Unfortunately, due to the inevitable effects of CHT, patients suffered from diarrhea, neutropenia, nausea, vomiting, asthenia, mucositis, fever and neuropathies.

Generally, the administration of 5-FU based protocols in 'Infusion form' had fewer problems manifesting itself as neutropenia, mucositis and diarrhea compared to the 'Bullous form'.

Therefore, it can be concluded, FOLFOX has the same issues. Built on this information, 6% of our cases had febrile neutropenia causing for admission and antibiotic therapy accompanying a GCSF (Colony Stimulation Factor). However, with FOLFIRI, the percentage of diarrhea was higher specifically in grade III and IV (17%) necessitating serum therapy and Leupromide®. But, in contrast, febrile neutropenia was detected just in one case with this regiment.

The occurrence of thrombocytopenia was perceived to be twice more with FOLFOX. Also, alopecia in grade I and II was observed in 48% of the cases. In just one patient, laryngeal paresthesia was observed which was managed by the use of diazepam. Neutropenia was one of the major complications of CHT, particularly with FOLFOX (just 4% with FOLFIRI). This problem was reduced by limiting the dosage of oxaloplatine in further cycles (Table-2, 3).

## Discussion

Although, the modalities of treatment in colo-rectal cancer have been impereceptubly ameliorating, various techniques conducted for its management. As an example, in some centers, palliative methods play a particular role for in controlling the symptoms and size of tumor. Providing better OS (overall survival) is a definitive objective for all of these approaches.

Fundamentally, early diagnosis, beyond a doubt, affords a better and more effective quality of life. Taking into consideration that, colo-rectal cancer has a tendency to demonstrate itself with a chronic feature, the performance status of patients individually through self- orientation and awareness combined with early diagnosis, assists them in having acceptable long survival rates.

Obviously, the commencing of treatment in a specific, detailed and structured time frame, with a constant regimen (FOLFOX or FOLFIRI) which is applied on a regular basis, validates a response with a better management of side effects, thus producing better survival rates. In other words, these two regimens have similar efficacy but different tolerability.In practice, FOLFIRI has been seen to produce less neuropathy. But, in our study, with respect to the synchronization between these two schedules, 8 cycles of treatment was designated for both.

Clearly, in debating the side effects of chemotherapy, it has great advantages in many aspects as a comparison with best supportive care.

## Conclusion

FOLFOX and FOLFIRI were precisely administrated in 8 cycles each concomitantly (sequential form) which provided considerable response with manageable complications.

The result of treatment in the study was correlated with other trials utilizing more modern procedures of medication like 'Target therapies' (OS; 18.4 months for CT versus 19-20 months for target therapies). It is clear that, CT has more advantages in term of cost and availability as the others.

Therefore, it is more efficient to perform 'Sequential method' in managing the patients.

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