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The role of FOLFOXIRI in chemorefractory metastatic colorectal cancer patients

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ABSTRACT

Introduction: The use of FOLFOXIRI (oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil) as first-line therapy for metastatic colorectal cancer (mCRC) is well-established. However, there is no data about the effectiveness of this regimen in pretreated patients in the current literature. In this case report, we aim to evaluate the efficacy and benefit of FOLFOXIRI in patients who received standard regimens.
Case report: 3 patients were treated with FOLFOXIRI and 1 patient received FOLFOXIRI + bevasizumab. Three patients had a partial response to FOLFOXIRI; one of these patients showed disease progression on this chemotherapy regimen and died. Progression free survival (PFS) of three patients was 5.5, 9 and 7.5 months respectively. One patient showed progression without any response to treatment.
Conclusion: We observed a partial response in 3 patients who were treated with FOLFOXİRİ and their progression-free survival was more than 3 months. These patients were treated with FOLFOXİRİ as a third or fourth line therapy. FOLFOXIRI should be considered as an alternative option in patients who have received standard treatments with good performance status.

1. Introduction

Approximately 20 percent of colorectal cancer (CRC) patients have distant metastatic disease at the time of presentation. Most patients with mCRC have incurable disease, although a subset of patients with limited metastases are potentially curable with surgery. For other patients with mCRC, treatment is palliative and usually consists of systemic chemotherapy.[1] We analysed the efficacy of the FOLFOXIRI regimen for the third or fourth line treatment of four mCRC patients refractory to five major drugs; irinotecan, oxaliplatin, 5-FU, bevacizumab and cetuximab (for K-Ras wild type tumor; patient 4). The FOLFOXIRI regimen consists of oxaliplatin (85 mg/m^2), irinotecan (165 mg/m^2), leucovorin (400 mg/m^2) on day 1, followed by a 46 hour infusion of 5-fluorouracil (5-FU) (1600–2400 mg/m^2) ± bevacizumab (5mg/kg) on day 1 (14-day cycle).

2. Case report

Three of four patients were treated with FOLFOXIRI and one received FOLFOXIRI + Bevasizumab (Patient 2). One of these patients had received FOLFOXIRI as 4th line treatment (Patient 1) and the others had FOLFOXIRI as 3rd line treatment. Patient 2 had received regorafenib after progression and patient 1 had received raltitrexed before progression on FOLFOXIRI. Three patients had partial response to FOLFOXIRI; one of these patients showed progression on this triplet chemotherapy regimen and died (Patient 1). The other patient was still being treated with FOLFOXIRI (Patient 4) and the last one was receiving regorafenib after progression on FOLFOXIRI (Patient 2). PFS of these three patients was 5.5, 9 and 7.5 months respectively. One patient showed progression with no response to treatment with a PFS of 3 months and died soon after (Patient 3). In patient 2, bevacizumab was added to the FOLFOXIRI protocol because of the long PFS of first-line bevacizumab monoclonal antibody in combination with doublet chemotherapy. Patients 1 and 3 had relatively short progression-free survival and the progression-free survival time of these patients was also short during their previous treatment. While patient 3 had right-sided colon cancer, the remaining patients had left-sided colon cancer. Patients 2 and 4 had comparatively long progression free survival

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Table 1
Patient and tumor characteristics and treatment details.

	Patient 1	Patient 2	Patient 3	Patient 4
Age	61	67	51	64
ECOG	1	0	1	0
Treatment	FOLFOXIRI	FOLFOXIRI + Bevacizumab	FOLFOXIRI	FOLFOXIRI
Treatment Line	Fourth	Third	Third	Third
K-Ras	Mutant	Mutant	Mutant	Wild
B-Raf	Wild	Wild	Wild	Wild
PFS1 and first line chemotherapy	3 months FOLFIRI + Bevacizumab	12 months XELOX + Bevacizumab	3 months FOLFOX + Bevacizumab	12 months FOLFOX + Bevacizumab
PFS2 and second line chemotherapy	3 months FOLFOX + Bevacizumab	3 months FOLFIRI + Bevacizumab	3 months FOLFIRI + Bevacizumab	3 months FOLFIRI + Cetuximab
PFS3 and third line chemotherapy	3 months Raltitrexet	7.5 months FOLFOXIRI + Bevacizumab	3 months FOLFOXIRI	>9 months FOLFOXIRI
PFS4 and fourth line chemotherapy	5.5 months FOLFOXIRI	2 months Regorafenib		
Site of primary tumour	Left-sided	Left-sided	Right-sided	Left-sided
Previous therapy with anti EGFR	No	No	No	Yes
Metastatic sites	Liver and Peritoneal	Lung	Liver	Liver
PFS (Months)	5.5 months	7.5 months	3 months	>9 months
RR	PR→PD	PR→PD	PD	PR
Prognosis (After FOLFOXIRI)	Died of disease	Progresive disease (Regorafenib)	Died of disease	FOLFOXIRI

PFS: Progression-free survival, **RR:** Response rate, **PD:** Progressive Disease, **PR**: Partial Response.

times. While patient 1 had liver and peritoneal metastases, patients 3 and 4 had only liver metastases and patient 2 had lung metastases in addition (Table 1). The most common grade 3–4 haematological and non-haematological treatment-related toxicities were neutropenia and diarrhea. Two patients had neutropenia grade 3 or higher and one patient had grade 3 diarrhea. Two patients required dose reduction. Since neutropenia persisted despite dose reduction in one patient, prophylactic colony-stimulating factor was added during subsequent cycles.

3. Discussion

There have been two phase 3 trials of FOLFOXIRI in the first-line treatment of mCRC. In a study conducted by Falcone A et al., median overall survival (OS) was superior with FOLFOXIRI compared with FOLFIRI although there is no statistically significant difference regarding OS between two regimens in the HORG trial (3). However, to our knowledge there are no randomized prospective or retrospective studies that have evaluated the activity of FOLFOXIRI in third or fourth line treatment. FOLFOXIRI was administered to patients who had received FOLFOX or FOLFIRI as first or second line treatment in order to overcome resistance to these drugs and to increase their efficacy.[2,3] Although the standard treatment in chemotherapy refractory mCRC patients consists of regorafenib, we could not supply regorafenib in our country during that period of time. Regorafenib improved overall survival 1.4 months when compared to placebo in a phase 3 study with a disease control rate (DCR) of 41%. Similar to regorafenib[4] TAS-102 also showed survival benefit and high DCR (44%) in comparison with plasebo.[5]

As previously mentioned, FOLFOXIRI has been administered as first line treatment in two phase 3 trials[2,3] and resulted in PFS of 9.8 and 8.4 months. In our trial, patients received FOLFOXIRI as third or fourth line therapy and their PFS was 9, 7.5, 3 and 3 months, respectively. Of note, the patients with longer PFS (9 and 7.5 months) also exhibited longer PFS during previous treatment. Furthermore, both of these patients had isolated sites of metastases (in the liver and lung, respectively). The two patients with shorter PFS had right colon and peritoneal metastases, respectively, which are both predictors of poor prognosis.[6,7] These two patients also had shorter PFS during previous treatment.

We observed a partial response in three out of four patients and PFS of longer than 3 months in all patients when FOLFOXIRI was used for third or fourth line treatment. We currently have a limited number of options in mCRC patients resistant to conventional therapies. For this reason, FOLFOXIRI should be considered as an alternative option in patients with good performance status who have received standard treatments.

References

1. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med*. 2012;367:1616.
2. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670–1676.
3. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer*. 2006;94:798–805.
4. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303–312.
5. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909–1919.
6. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol*. 2012;30:263–267.
7. Benedix F, Kube R, Meyer F, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum*. 2010;53:57–64.