

## Response to Chemotherapy in Metastatic Colorectal Cancer After Exposure to Oxaliplatin in the Adjuvant Setting

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**Abstract.** *Aim: Oxaliplatin with 5-fluorouracil (5-FU) and leucovorin (FOLFOX and FLOX) or capecitabine (XELOX) is the standard adjuvant treatment for colonic cancer. In metastatic disease, 5-FU/leucovorin/irinotecan (FOLFIRI) and FOLFOX are equivalent in respect to response rates, progression-free and overall survival. Little data are available to compare their efficacy after exposure to oxaliplatin-containing adjuvant chemotherapy. Patients and Methods: We carried out a retrospective study of patients who underwent surgery and FOLFOX adjuvant chemotherapy, followed by FOLFIRI or FOLFOX for metastatic disease. Exclusion criteria were: metastatic disease at presentation and no oxaliplatin in adjuvant chemotherapy. The end-point was the overall response rate (ORR) to first-line chemotherapy for metastatic disease after three months, as assessed by computed tomography (CT). Results: A total of 205 patients received FOLFOX as adjuvant treatment for colorectal adenocarcinoma between 2006 and 2010. Metastatic disease was diagnosed later in 32 cases after a median follow-up of three years (range=1-5.5 years). The median time between the beginning of adjuvant chemotherapy and onset of metastatic disease was 1.7 years (range=0.5-5.5 years). Twenty-eight patients were evaluable for effects of treatment: six patients received FOLFOX plus bevacizumab and 22 FOLFIRI plus bevacizumab. The ORR was 17% in the FOLFOX group versus 36% in the FOLFIRI group ( $p=0.22$ ). This difference was not statistically significant, despite a trend in favor of*

*FOLFIRI. Conclusion: Metastatic disease after exposure to oxaliplatin in the adjuvant setting tends to occur early and can be characterized by partial resistance to this agent. Despite insufficient statistical power, our results suggest that FOLFIRI may result in higher response rates than FOLFOX in this situation. However, oxaliplatin re-challenge can also lead to radiological responses and disease stabilization.*

Colorectal cancer is the third most common primary malignancy and is the second cause of cancer-related deaths in industrialized countries (1). The mainstay of treatment for localized disease is surgical resection followed by adjuvant chemotherapy for 6 months in stage III tumors, as chemotherapy improves cure rates (2). Adjuvant chemotherapy is less well-established in stage II, but is considered acceptable in high-risk situations (3).

For decades, adjuvant chemotherapy for colonic cancer only consisted of 5-FU and leucovorin, which were administered together according to a variety of schedules. Capecitabine, an oral pro-drug form of 5-FU, was subsequently found to be equivalent in efficacy to 5-FU/leucovorin in the adjuvant setting (4). However, the addition of oxaliplatin to either 5-FU or capecitabine significantly improves disease-free and overall survival of patients with colonic cancer who have undergone curative-intent surgery: follow-up data of the pivotal MOSAIC trial show 6-year overall (OS) survival rates of 72.9% and 68.7%, respectively, in patients treated with adjuvant FOLFOX or 5-FU/leucovorin-alone (5).

For metastatic disease, commonly used regimens are combinations of fluoropyrimidines such as 5-FU or capecitabine with either irinotecan or oxaliplatin, in addition to bevacizumab or antibodies against EGFR. There is no significant difference in terms of efficacy between FOLFIRI and FOLFOX, as shown by two randomized trials (6, 7), and selection of one or the other regimen often depends on patients' comorbidities, institutional or personal preferences. After progression on first-line treatment, patients can benefit from the alternate regimen in second line. However, these

\*Presented, in part, in abstract form at the European Multidisciplinary Colorectal Cancer Conference in April 2012, in Prague (Czech Republic).

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**Key Words:** Adjuvant treatment, chemotherapy, colorectal cancer, oxaliplatin, metastatic disease.

Table I. Response rates of first-line regimens.

	CR: n/N (%)	PR: n/N (%)	SD: n/N (%)	PD: n/N (%)
FOLFOX + Bevacizumab	0/6 (0%)	1/6 (17%)	3/6 (50%)	2/6 (33%)
FOLFIRI + Bevacizumab	0/22 (0%)	8/22 (36%)	10/22 (45%)	4/22 (19%)

clinical trials were performed when oxaliplatin was not yet accepted as part of standard adjuvant chemotherapy. Therefore, the optimal first-line regimen for metastatic colorectal cancer after oxaliplatin-containing adjuvant chemotherapy is not defined. Given the relatively low risk of recurrence after adjuvant chemotherapy, a randomized trial to explore this question is difficult to perform. A retrospective study was designed to compare response rates between FOLFOX and FOLFIRI in patients with metastatic disease after oxaliplatin-containing adjuvant chemotherapy for colorectal cancer.

## Patients and Methods

After approval from the McGill University Health Centre Research Ethics Board, the database of the hospital pharmacy was used to identify all patients who received oxaliplatin as adjuvant treatment for colorectal cancer. In order to have adequate follow-up data, the analysis was restricted to patients treated between 2006 and 2010. A chart review was then conducted to identify patients diagnosed with colon or rectal adenocarcinoma who were treated with FOLFOX or FOLFIRI in the metastatic setting after receiving an adjuvant oxaliplatin-containing regimen with a curative intent. Exclusion criteria included other tumor histology or primary site, metastatic disease at presentation, no surgery for the primary tumor, previous adjuvant chemotherapy without oxaliplatin, and absence of adjuvant chemotherapy. After three months, patients were restaged with CT of the chest, abdomen and pelvis, and determined to have complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The endpoint of interest was the difference between FOLFIRI and FOLFOX-treated groups in regards to overall response rate (ORR=CR+PR). The Chi-square test was used to compare different response categories between the two groups.

## Results

Between 2006 and 2010, 204 patients received FOLFOX as adjuvant treatment for colonic or rectal adenocarcinoma after surgical resection of the primary tumor. The median age at diagnosis of colorectal cancer was 62 years. The primary tumor was localized in the colon in 21 patients (66%), and the rectum in 11 cases (34%). Initial staging was stage II in three patients (9%) and stage III in 29 (91%) Metastatic disease was subsequently diagnosed in 32 cases (19 males, 13 females) after a median follow-up of three years (range 1-

5.5 years), yielding a disease-free survival of 84%. The median time between the beginning of adjuvant chemotherapy and the onset of metastatic disease was 1.7 years (range=0.5-5.5 years). In addition to surgery, seven patients received neoadjuvant chemo-radiotherapy with 5-FU for rectal adenocarcinoma (22%).

Out of 32 patients with relapse, four were excluded from analysis for the following reasons: non-administration of chemotherapy for metastatic disease (n=2); capecitabine monotherapy at time of recurrence (n=1); missing data (n=1). Twenty-eight patients were therefore included in the analysis for the effects of treatment: six patients received FOLFOX plus bevacizumab and 22 FOLFIRI plus bevacizumab. Reasons for the choice of the first-line regimen were not consistently documented, but included persistent neuropathy from exposure to oxaliplatin. Descriptive results are presented in Table I. ORR was 17% in the FOLFOX/bevacizumab arm and 36% in the FOLFIRI/bevacizumab arm ( $p=0.22$ ). Clinical benefit rate, defined as the sum of response and stable disease (SD) rates were 67% in the FOLFOX arm and 81% in the FOLFIRI arm ( $p=0.28$ ). Time-to-progression could not be adequately measured as CT scans were not performed at the same frequency for all patients. At last follow-up, nine patients had died from their disease (35%), 15 were alive with disease (58%) and two were alive without disease, after metastatectomy (8%). Activity of FOLFOX (without bevacizumab) was also seen in second line, after progression on FOLFIRI: of five patients, one experienced partial response followed by pulmonary metastatectomy; another had prolonged disease stabilization (15 months) on FOLFOX plus an experimental antiangiogenic antibody.

## Discussion

This study aimed at comparing real-life radiological response data between FOLFIRI/bevacizumab and FOLFOX/bevacizumab for metastatic colorectal cancer after prior exposure to oxaliplatin in the adjuvant setting. It must be noted that until 2013, anti-EGFR therapy was not approved in Canada for first-line therapy in combination with cytotoxic chemotherapy. Although the superiority of FOLFIRI over FOLFOX was not demonstrated, probably

because of a lack of statistical power, it appears plausible that FOLFIRI could produce a higher response rate, as earlier exposure to oxaliplatin-containing adjuvant chemotherapy may have favored the emergence of oxaliplatin-refractory disease at the time of recurrence. However, this resistance is not absolute, as suggested by examples of activity of FOLFOX in both the first and second lines of treatment of metastatic disease. Because of small patient numbers, we were not able to carry out sub-group analyses to investigate the impact of duration of disease-free interval on the efficacy of FOLFOX after relapse. This question is important in other malignancies treated with platinum-derived agents such as ovarian cancer (8).

One well-documented mechanism of resistance to oxaliplatin in the metastatic setting is overexpression of ERCC1 and ERCC2, DNA repair enzymes (9). This overexpression can be intrinsic or acquired. Attempts to link polymorphisms of genes coding for these enzymes and efficacy of adjuvant oxaliplatin have not been successful (10). Concomitant use of biological agents with oxaliplatin may prevent or reverse resistance to oxaliplatin, an effect that may be relevant to our patient population.

An interesting observation is the rapid time-to-relapse after adjuvant chemotherapy in the patients we studied. The time interval between the beginning of adjuvant chemotherapy and the occurrence of metastatic disease averaged 1.7 years, suggesting that the median time-to-recurrence after completion of FOLFOX adjuvant chemotherapy was only one year, assuming a 6-month course of treatment. Another potential mark of disease aggressiveness could be the low response rates to first-line chemotherapy, regardless of the regimen chosen, in comparison to reported rates in the literature in patients not previously exposed to oxaliplatin (6). However, this interpretation must be tempered by the small number of patients studied, and the overall prognosis of these patients should be estimated from registries of major clinical trials of adjuvant chemotherapy of colorectal cancer.

Given the difficulty of designing a clinical trial to address the question of interest, our effort resulted in a retrospective study with a small, but complete, sample of patients from a single institution. Moreover, the sub-group who received oxaliplatin in the metastatic setting was much smaller than the sub-group who received irinotecan, which may have limited the accuracy of our statistical analyses. Nonetheless, we believe that our study gives clinically useful data that could be used as part of the background information for future trials.

## Conclusion

Although we cannot, in a definitive way, demonstrate the superiority of FOLFIRI/bevacizumab over FOLFOX/

bevacizumab in patients with metastatic colorectal cancer previously-exposed to oxaliplatin in the adjuvant setting, our results do suggest a higher response rate with the former regimen. However, resistance to oxaliplatin may not be complete, as shown by the occurrence of radiological responses in the first and second lines of treatment. Experiments investigating strategies to reverse this resistance to oxaliplatin would be important, given the present incurability and limited options of patients with unresectable metastatic colorectal cancer.

## Conflicts of Interest

None.

## Acknowledgements

This study was supported by a research grant from Sanofi-Aventis Canada. Dr. Alcindor is the recipient of a Henry R. Shibata Fellowship at Cedars Cancer Institute, Montreal, QC.

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*Received February 19, 2013*

*Revised March 16, 2013*

*Accepted March 19, 2013*