

# World Journal of *Gastroenterology*

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- 1847** Malignant gastric outlet obstruction: Which is the best therapeutic option?  
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- 1861** Macrophages in metabolic associated fatty liver disease  
*Alharthi J, Latchoumanin O, George J, Eslam M*

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- 1888** Sequencing of systemic treatment for hepatocellular carcinoma: Second line competitors  
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- 1901** Therapeutic advances in non-alcoholic fatty liver disease: A microbiota-centered view  
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- 1926** Mutation analysis of related genes in hamartoma polyp tissue of Peutz-Jeghers syndrome  
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- 1938** Iron metabolism imbalance at the time of listing increases overall and infectious mortality after liver transplantation  
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- 1971** Severe steroid refractory gastritis induced by Nivolumab: A case report  
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- 1979** Efficacy of bevacizumab-containing chemotherapy in metastatic colorectal cancer and CXCL5 expression: Six case reports  
*Novillo A, Gaibar M, Romero-Lorca A, Gilsanz MF, Beltrán L, Galán M, Antón B, Malón D, Moreno A, Fernández-Santander A*

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## Efficacy of bevacizumab-containing chemotherapy in metastatic colorectal cancer and CXCL5 expression: Six case reports

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### Abstract

#### BACKGROUND

In metastatic colorectal cancer (mCRC), the anti-vascular endothelial growth factor drug bevacizumab (BVZ) plus chemotherapy significantly improves progression-free survival compared to chemotherapy (CT) alone. This benefit is not, however, observed in all patients. While increased chemokine CXCL5 gene expression promoting angiogenesis has been proposed as a prognostic mCRC biomarker, few studies have examined its relationship with drug efficacy. This study sought to analyze tumor CXCL5 gene expression in six patients with different efficacy of BVZ-containing CT in terms of the tumor response to treatment.

#### CASE SUMMARY

We report six cases of stage IV KRAS-mutated mCRC. Patients were given first line treatment with BVZ-containing chemotherapy in University Hospital of Fuenlabrada. The six patients differed in terms of primary tumor location (right/left side), tumor burden (mostly hepatic and peritoneal disease) and clinical disease course. Before treatment onset, total RNA was isolated from paraffinated tumor biopsy specimens and CXCL5 gene expression quantified

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through conventional RT-qPCR procedures. Our main finding was that CXCL5 expression levels were several times higher in three patients with lower progression free survival (under 6 mo) from the start of treatment.

## CONCLUSION

A higher expression of CXCL5 was observed in the three patients showing worse tumor response to treatment.

**Key words:** Colorectal cancer; Bevacizumab; Chemokine CXCL5; Gene expression; Progression-free survival; Case report

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**Core tip:** Although compared to chemotherapy (CT) alone, bevacizumab-containing CT leads to a significantly better tumor response in metastatic colorectal cancer patients, many do not benefit from this regimen probably due to resistance mechanisms or readjustment of proangiogenic pathways. While CXCL5 expression has been described to predict a poor prognosis in different cancers, its relationship with the efficacy of CT regimens has been scarcely addressed. Our three patients showing CXCL5 higher expression (6 times the levels recorded in the others) showed a poor response in terms of progression-free survival. Our observations provide direction for future studies designed to examine in metastatic colorectal cancer patients treated with bevacizumab-containing therapy, the possible association between CXCL5 gene overexpression and a poor response to treatment with angiogenic drugs.

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## INTRODUCTION

Angiogenesis is essential for tumor growth. It has been established that the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) play major roles in angiogenesis associated with advanced cancer. The monoclonal antibody bevacizumab (BVZ), an anti-VEGF drug directed against the vascular endothelium, is a common component of combination chemotherapy (CT) regimens used in patients with metastatic colorectal cancer (mCRC). Several authors have reported significant improvements in progression-free survival (PFS), overall survival (OS) and response rate in mCRC patients compared to CT alone<sup>[1,2]</sup>. However, in a significant number of patients there is no meaningful benefit probably because of the acquisition of resistance mechanisms involving activation of compensatory proangiogenic pathways or tumor recruitment of cells that produce proangiogenic factors<sup>[3]</sup>.

CXCL5 is a chemokine that binds the G-protein-coupled receptor chemokine receptor 2 (CXCR2) to recruit neutrophils, promote angiogenesis and remodel connective tissues, playing a role in cancer cell proliferation, migration, and invasion<sup>[4,5]</sup>. While several studies during the past decade have examined the use of CXCL5 gene expression as a biomarker for cancer diagnosis or prognosis, *e.g.*, Wu *et al*<sup>[6]</sup>, few investigations have explored the relationship between CXCL5 expression and treatment efficacy. In this paper, we describe six patients with mCRC who showed a different response to BVZ-containing CT, and discuss the possibility of a relationship between differential CXCL5 tumoral gene expression and the efficacy of the regimen used in terms of PFS.



## CASE PRESENTATION

### **Chief complaints**

We identified six Caucasian patients with metastatic colorectal cancer. There were 3 men and 3 women with a median age of 70 years at diagnosis (range: 47-81 years). Patient characteristics are summarized in Table 1. The patients were referred to department of oncology for clinical and therapeutic evaluation.

### **History of present illness**

Each case was diagnosed due to slightly different symptoms, some of them related:

**Case 1:** This was a 62-year-old woman who was studied from aggravated constipation, tenesmus, abdominal pain and rectal bleeding in November 2012 with stage IV KRAS-mutated rectal cancer with a low disease burden (lung and liver metastasis).

**Case 2:** This patient was a 47-year-old presented at the emergency room with acute abdominal pain less than 48 h in right iliac pit in September 2016. She suffered bowel obstruction and required left colectomy, adnexectomy and cytoreduction. She was diagnosed with stage IV (metastases in peritoneum, ovary, liver) KRAS-mutated sigmoid cancer.

**Case 3:** A 71-year-old man was studied due to weight loss and occasional vomiting for few months in December 2015. He was diagnosed with stage IV (liver metastases), KRAS-mutated, right colon cancer.

**Case 4:** A 62-year-old man, who was diagnosed with a right KRAS-mutated colon tumor with lung metastasis in May 2011. He presented with diarrhea and weight loss for 6 months.

**Case 5:** This case was an 81-year-old man with stage IV, KRAS-mutated sigmoid cancer (lung metastasis) who underwent primary tumor resection in February 2014. He debuted with rectal bleeding for few weeks before without pain or weight loss.

**Case 6:** The final case was that of a 75-year-old woman who was diagnosed in March 2015 with mucinous appendix KRAS-mutant colon cancer. She was admitted due to right iliac pit pain and increased abdominal size for two months.

### **History of past illness**

**Case 1:** Her personal background consisted of high blood pressure, hypercholesterolemia and osteoporosis.

**Case 2:** She presented severe sleep apnea-hypopnea syndrome, multinodular goiter and uterine myomas.

**Case 3:** He had high blood pressure and hypercholesterolemia under treatment with optimal control.

**Case 4:** His clinical record was only based on pulmonary tuberculosis and nodular hyperplasia of thyroid.

**Case 5:** He presented just hypercholesterolemia and chronic lumbalgia.

**Case 6:** Unremarkable.

### **Personal and family history**

**Case 1:** She had one brother with gastrointestinal stromal tumor and father with lung cancer and smoking story.

**Case 2:** Her father had sigmoid cancer and her mother suffered of breast cancer.

**Case 3 and 4:** Unremarkable.

**Case 5:** Deceased father with colon cancer at 70 years old and one living brother with previous rectal cancer diagnosed with 80 years-old.

**Case 6:** Unremarkable.

### **Physical examination upon admission**

**Case 1:** Her vitals were normal as well as cardiopulmonary auscultation. She had only lower abdominal pain at hypogastric region.

**Table 1 Patient characteristics**

Characteristics	Data (n = 6)
Gender	
Male	3 (50)
Female	3 (50)
Age (yr)	70 (47-81)
Tumor stage IV <sup>1</sup>	6 (100)
Localization <sup>1</sup>	
Right	2 (33.3)
Sigmoid	2 (33.3)
Rectal	1 (16.7)
Mucinous appendix	1 (16.7)
KRAS status <sup>1</sup>	
Mutated	6 (100)
Normal	0 (0)

<sup>1</sup>Evaluated before chemotherapy. Data are n (%).

**Case 2:** She presented pain in the upper abdominal quadrant and associated peritonism.

**Case 3:** He presented with abdominal pain without peritonism.

**Case 4:** Vitals were normal, no abdominal pain, masses palpation or peritonism.

**Case 5:** He just presented discrete abdominal pain, without any other signs.

**Case 6:** She presented with shortness of breath due to mechanical impingement on the diaphragm. Besides physical examination of the abdomen presented bulging of the flanks and shifting dullness, and edema in lower legs.

### Laboratory examinations

**Case 1:** Blood test without abnormalities except from high level of carcinoembryonic antigen (CEA) 29.7 ng/mL (0.5-5).

**Case 2:** She presented high levels of serum markers CEA 83.7 ng/mL and carbohydrate antigen (CA19.9) 84 UI/mL (0-35) and anemia hemoglobin 10.5 g/dL.

**Case 3:** Blood test with anemia 11 g/dL and high CEA 69.7 ng/mL.

**Case 4:** His blood test presented hemoglobin 12.5 g/dL with low ferritin and normal serum markers.

**Case 5:** Blood test was normal without anemia or high serum markers.

**Case 6:** Hemoglobin 11.8 g/dL and serum markers CEA 930 ng/mL and CA 19.9 75 UI/mL.

**Case 1-6:** Before treatment onset, total RNA purification was performed on paraffinated tumor tissue biopsy specimens using Promega kits and Maxwell techniques from three five  $\mu$ m-slices. CXCL5 gene expression was quantified through conventional RT-qPCR techniques (Biorad). The housekeeping gene *G3PDH* was used to normalize CXCL5 gene expression. Table 2 displays normalized gene expression for CXCL5 gene from each biopsies and PFS after BVZ-containing treatment onset. The three patients showing CXCL5 higher expression (6 times the levels recorded in the others) showed a poor response in terms of PFS (Table 2).

### Imaging examination

**Case 1:** Computed tomography was performed at the beginning of diagnosis with rectal tumor in radiological stage T3N1M1 with multiple hypodensive lesions, in both lobes and pulmonary nodules.

**Case 2:** Computed tomography showed sigma neoplasm with hepatic metastatic disease, apart from multiple local adenopathies. Besides, complex cystic mass in right ovarian of 13 cm  $\times$  10 cm was presented that could be compatible with ovarian



**Table 2** Normalized CXCL5 gene expression levels and progression-free survival after bevacizumab-containing treatment onset in the six cases reported in this study

Case number	1	2	3	4	5	6
PFS after BVZ-containing treatment onset (mo)	18	12	12	3	6	3
Overall PFS after BVZ-containing treatment onset (mo)	12 (12-18)			3 (3-6)		
Normalized CXCL5 gene expression	10.700	3.655	0.002	23.430	20.390	32.900
Overall normalized CXCL5 gene expression	3.655 (0.002-10.700)			23.430 (20.390-32.900)		

Overall data are median (range). BVZ: Bevacizumab; PFS: Progression-free survival.

metastases.

**Case 3:** Colonoscopy showed mass in right colon with stenotic diameter. Besides computed tomography was performed to confirm colon cancer stage T4a N1 M1 with regional adenopathies, peritoneal implants with ascites and three metastatic liver lesions.

**Case 4:** Computed tomography presented right colon tumor in radiological stage T4 N1 M1 with regional adenopathies and two nodules in right lung lobe.

**Case 5:** Colonoscopy showed neoformation that occupied more than 90% up to 30 cm of anal margin where the light did not allow the endoscope to pass. Computed tomography scan confirmed sigma stenosis tumor with radiological stage T3N2M1 due to lung nodules.

**Case 6:** Computed tomography scan showed signs of extensive pseudomyxoma and inframesolic secondary to mucinous colon carcinoma with abundant ascites and peritoneal implants and small bowel infiltration.

## FINAL DIAGNOSIS

The final diagnosis of the six presented cases was stage IV KRAS-mutated colorectal cancer.

## TREATMENT

### Case 1

Treatment was 5-fluorouracil and irinotecan (FOLFIRI) plus BVZ for 8 cycles, to which she showed a partial response, short-course preoperative radiotherapy, and two surgeries (first for the primary tumor, interval CT for two cycles without an antiangiogenic molecule and then left hepatectomy and radiofrequency ablation in the right liver lobe). She was maintained on the same CT regimen until lung progression detected 18 mo after diagnosis, and therapy was switched to FOLFOX (oxaliplatin, 5-fluorouracil, leucovorin). The response was rapid disease progression. For one year, she received third line treatment with FOLFIRI plus aflibercept until bone metastasis in October 2014. She then underwent radiation therapy and was started on fourth line regorafenib.

### Case 2

She started on FOLFOX plus BVZ for 8 cycles with a partial response. A right hepatectomy and ALPSS procedure (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) were performed in May 2017 requiring long hospitalization. In total, she received 13 CT cycles. In October 2017, she was readmitted because of peritonitis but two months later there was disease progression. This patient received second line treatment with FOLFIRI-aflibercept for six months to which she responded.

### Case 3

Treatment was FOLFOX plus BVZ for 3 cycles plus advanced surgery because of bowel blockage. The patient received 12 doses of this BVZ-containing CT and there was no evidence of disease during 12 mo. In March 2017 he was treated with radiofrequency ablation and FOLFIRI-aflibercept CT because of hepatic relapse, to

which he responded; in December 2018 he underwent cytoreductive surgery.

#### Case 4

He was first given 4 cycles of FOLFOX without bevacizumab due to a risk of bowel perforation. Three months later, the disease progressed and he underwent surgery for the primary colon tumor because it was symptomatic. Following three months of further CT based on FOLFIRI plus BVZ with no response, he was switched back to FOLFOX with the same anti-VEGFR for 8 cycles more.

#### Case 5

He completed adjuvant treatment with capecitabine for only 3 mo due to cardiac ischemia. In August 2014, there was lung and lymph disease progression, so he was started on capecitabine plus BVZ for 12 cycles.

#### Case 6

She was treated with hyperthermic intraperitoneal CT surgery and first-line CT based on FOLFOX plus BVZ for 13 cycles resulting in disease stabilization. This was followed by treatment with 5-fluorouracil plus BVZ due to neurotoxicity and myelotoxicity until progression in December 2015. She continued with FOLFIRI plus BVZ with progression observed after 3 mo and several hospitalizations required due to acute pain. Finally, the patient received third line TAS102 (trifluridine/tipiracile).

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## OUTCOME AND FOLLOW-UP

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#### Case 1

In January 2016 she was admitted to hospital due to acute exacerbation of chronic pain, clinical worsening and died at 66 years.

#### Case 2

She was hospitalized due to liver failure (in February 2018) and died.

#### Case 3

Currently he is well and there is no evidence of disease at 74 years-old.

#### Case 4

He did not show improvement and finally died in May 2012.

#### Case 5

The treatment capecitabine plus BVZ for 12 cycles was ineffective and lung involvement progressed until death in August 2016 at 84 years-old.

#### Case 6

The response was rapid tumor progression until her death in July 2017.

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## DISCUSSION

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Colorectal cancer is the most common gastrointestinal tract cancer and is associated with a high morbidity and mortality in both men and women<sup>[7]</sup>. Both its early detection and the search of targeted therapies are critical for improving outcomes and reducing CRC patient mortality. Biomarkers for diagnosis, prognosis and targets of therapy are urgently needed to improve survival rates. According to current guidelines, a first-line treatment option for mCRC is the combination of BVZ plus CT consisting of 5-fluorouracil and oxaliplatin or irinotecan, especially in patients with the KRAS-mutated form of disease<sup>[8]</sup>. However, there is no general consensus as to whether patient selection for this treatment should be based only on KRAS status or whether other clinical characteristics (primary tumor site, histologic subtype, *etc.*) should be also taken into account<sup>[9]</sup>. Further factors that should also be considered are molecular markers of CRC as they could play a determining role in tumor progression. Unfortunately, these have not yet been identified.

Although BVZ antiangiogenic therapy is considered a good treatment option for mCRC, there is still scarce knowledge regarding its efficacy and resistance acquisition among patients. Reports exist in the literature on the benefits of BVZ-containing CT over CT alone in terms of significantly better PFS and OS detected in mCRC patients<sup>[2,10]</sup>. However, only 61% of mCRC patients treated with BVZ-containing CT show an objective response (complete or partial)<sup>[10]</sup>. It remains to be determined why some tumors prove resistant to BVZ either from the start of treatment or after several

months.

Chemokines produced by tumor and stromal cells are involved in the distribution of tumor-associated leukocytes, metastasis, angiogenesis and tumor growth<sup>[11]</sup>. The chemokine CXCL5, also called epithelial neutrophil-activating peptide 78-ENA-78-, binds the G-protein CXCR2 to recruit neutrophils and to promote angiogenesis, playing a role in cancer cell proliferation, migration, and invasion<sup>[12]</sup>. Because of the important role played by these molecules in cancer processes, several chemokines have been measured in different types of tumors, and abnormal expression levels observed in many of them (*e.g.*, Samarendra *et al.*<sup>[13]</sup>). The elevated expression of CXCL5 has been associated not only with gastric cancer, prostate cancer, endometrial cancer, squamous cell cancer, hepatocellular carcinoma and pancreatic cancer, but also with advanced tumor stages and with metastatic potential<sup>[14]</sup>. Several studies addressing the use of differential CXCL5 gene expression as a biomarker for cancer diagnosis or prognosis have been published in the past decade, *e.g.*, Wu *et al.*<sup>[6]</sup>. However, the relationship between CXCL5 expression and drug efficacy has been scarcely investigated. Sunitinib is a multitarget tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma. In this setting, plasma CXCL5 levels have been associated with therapy efficacy, but no correlation was found with BVZ-containing CT by Giuliano *et al.*<sup>[15]</sup>. The authors Li *et al.*<sup>[16]</sup> reported the down-regulation of another chemokine, CXCL1, in carcinoma-associated fibroblasts isolated from breast tumors as possibly responsible partially for the efficacy of letrozole, a non-steroidal aromatase inhibitor.

Germline genetic variability within genes related to the angiogenesis pathway could be associated with differences in resistance to anti-angiogenesis therapy among patients. de Haas *et al.*<sup>[17]</sup> studied SNP variants of *VEGF-C*, *EPAS1* and *CXCR2* genes in blood samples from patients treated with BVZ-containing CT. These authors identified the CXCR2 variant (rs2234671) as predictive of bevacizumab treatment outcome in terms of PFS. Wild-type CC carriers were characterized by prolonged PFS in different types of tumors such as colorectal, pancreatic, lung, renal, breast, and gastric. Gerger *et al.*<sup>[18]</sup> obtained similar results in a cohort of mCRC patients treated with BVZ and oxaliplatin-based CT.

Chen *et al.*<sup>[19]</sup> recently proposed that CXCL5 is an important angiogenic factor that can promote cell metastasis through tumor angiogenesis in CRC. This research group used recombinant human CXCL5 in *in vitro* experiments and observed enhancement of their tube formation ability, proliferation, and migration *via* activation of the AKT/NF- $\kappa$ B/FOXO1/VEGF-A pathway in a manner that was very dependent on CXCR2, the receptor of CXCL5. Besides, in *in vitro* studies, it was found that silencing of CXCR2 or these pathways could attenuate tube formation ability, proliferation, and migration. Similarly, increased CXCL5 expression was noted to augment microvessel density in an *in vivo* mouse tumor model. Thus, blocking overexpression of the CXCL5/CXCR2 axis could be a promising treatment strategy for CRC patients. These authors established a possible relationship between the CXCL5/CXCR2 pathway and VEGF-A expression. It is known that high plasma/intratumoral VEGF-A levels at baseline are related to a poor treatment response (reduced PFS and OS) to BVZ-based chemotherapy in mCRC<sup>[20]</sup>.

CXCL5 could be considered a significant predictor of tumorigenesis and progression because of the relationship observed between its overexpression and enhanced angiogenic pathway activity. Although CXCL5 expression has been described as a predictor of a poor prognosis in different types of cancer (prostate, endometrial, hepatocellular, and pancreatic)<sup>[21]</sup>, the current lack of data determines a need to explore the possibility of a relationship between CXCL5 expression and anti-angiogenic drug efficacy. Our three patients showing CXCL5 higher expression showed a poor response in terms of PFS (Table 2). The number of cases described here is a clear limitation for statistical analysis, but we consider this result a starting point for larger-scale studies. The hypothesis that an anti-VEGF drug such as BVZ may not counteract the overstimulation of microvessels and the search of better strategies as, for instance, the possibility of inhibition of the CXCL5/CXCR2 pathway in CXCL5 overexpressed patients could be a very interesting point of view in future enlarged studies.

## CONCLUSION

Although it is known that CXCL5 is a vital angiogenic factor in different types of cancer, very little information is available regarding the effects of CXCL5 in angiogenesis related to CRC. In this study, six biopsies from patients with mCRC treated with BVZ-containing therapy were analyzed to quantify CXCL5 gene expression. Our main

finding was the higher expression of CXCL5 observed in the three cases showing the worst PFS. Our observations provide a starting point for future studies designed to examine the possible association between CXCL5 gene overexpression and a poor response to treatment with angiogenic drugs in mCRC patients.

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