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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pathologic complete response in metastatic right-sided colon cancer treated with panitumumab and FOLFOX4 chemotherapy regimen

Miljana Džunić[1], Ana Cvetanović[1,2], Ivan Petković[1,2], Ivana Todorović-Stojanović[3]

[1]University Clinical Centre of Niš, Clinic of Oncology, Niš, Serbia;
[2]University of Niš, Faculty of Medicine, Niš, Serbia;
[3]Pirot General Hospital, Pirot, Serbia

SUMMARY

Introduction Recommended biological agents for the first-line treatment of left-sided metastatic colorectal cancer (mCRC) without mutations in *RAS/BRAF* genes are cetuximab or panitumumab, while for right-sided mCRC bevacizumab is advised instead. For transversal colon mCRC the data about biological treatment efficacy is lacking. We present a patient with right-sided mCRC originated from transversal colon where panitumumab and chemotherapy treatment resulted in an excellent outcome.

Case outline A 56-year-old woman was diagnosed with transversal colon adenocarcinoma, without *RAS* genes mutations, with multiple liver metastases disseminated in both lobes. After the operation of the primary tumor, the patient was treated with panitumumab and FOLFOX4 chemotherapy regimen. After two months of treatment, the dramatic response was evident – The diameter sum of the target lesions decreased by 70.5%. After two more months of therapy, further decrease by 22.5% was evident. Liver metastases were operated on. Histopathology revealed fibrotic and necrotic tissue in all suspicious lesions, except in one focus, where adenocarcinoma was found, but with 90% of surrounding necrosis. Twelve months after liver surgery the patient is without signs of the progressive disease.

Conclusion Detailed comprehensive studies of genetic features of mCRC hold a key to personalized treatment options and better outcomes for patients with mCRC.

Keywords: colorectal cancer; panitumumab; transversal colon; liver metastases

INTRODUCTION

Colorectal cancer (CRC) is among the most frequent and the most fatal malignancies [1]. Despite efforts towards primary prevention, screening colonoscopy and faecal tests, more than a half of patients will have metastatic colorectal cancer (mCRC), which has poor prognosis [2]. Addition of targeted biological treatment to chemotherapy and integration of surgery into the treatment paradigm of mCRC have contributed to survival improvement [3], being over 2.5 years, and still improving by tailoring treatment according to new predictive markers, such as primary tumor localization [4].

Monoclonal antibodies that block epidermal growth factor receptor (EGFR), cetuximab and panitumumab, are the standard of care in the first-line treatment of mCRC without *RAS* genes' mutations, with proven benefit in the left-sided primaries [5]. For right-sided mCRC, monoclonal antibody that neutralizes vascular endothelial growth factor (VEGF), bevacizumab is recommended instead [3]. However, there is not enough evidence about anti-EGFR efficacy in transversal colon, which is in the middle but formally belongs to the right side [6]. We present a patient with right-sided mCRC originated from transversal colon, where the treatment with panitumumab and 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) chemotherapy resulted in an excellent outcome.

CASE REPORT

A woman, age 56, was examined due to symptoms of frequent abdominal cramps and bloating. Colonoscopy revealed circumferential occlusive tumor in the transversal colon, and histopathology of biopsy specimen proved adenocarcinoma. The patient was on antihypertensive therapy due to mild hypertension. Her family history was negative for hereditary cancer.

Multislice computed tomography (MSCT) of the abdomen showed liver with multiple metastases, maximal diameter of 40 mm in the right hepatic lobe and 35 mm in the left lobe (Figure 1). MSCT of the thorax was without secondary deposits. Abnormal laboratory findings were elevated aspartate aminotransferase (65 U/L; reference range 10–37 U/L), alanine aminotransferase (74 U/L; reference range 10–42 U/L) and carcinoembryonic antigen (CEA) (104.8 ng/ml; reference range 0–5 ng/ml).

Due to subocclusive symptoms, right hemicolectomy was performed. Histopathology revealed adenocarcinoma, grade 2–3, pathologic TNM stage was pT3, N2a, with six of 15 lymph nodes positive for cancer, and prominent lymphatic and vascular invasion. Mutation test by

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Correspondence to:
Miljana DŽUNIĆ
University Clinical Centre of Niš
Clinic of Oncology
48 Dr. Zoran Đinđić Boulevard
Niš 18000, Serbia
drmdzunic@gmail.com

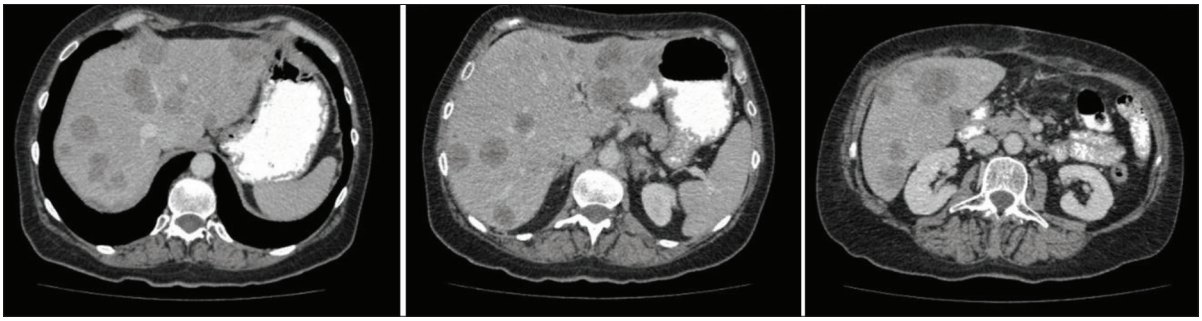


Figure 1. Multislice computed tomography before treatment, showing a liver with multiple metastases in both lobes, maximal diameter being 40 mm

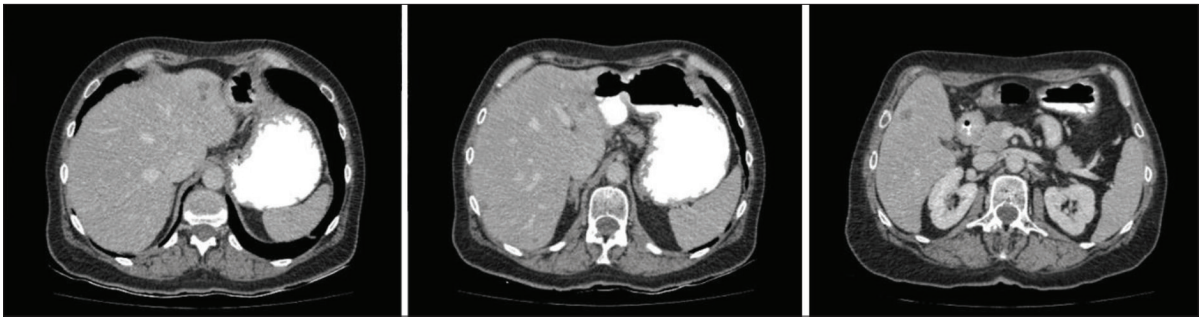


Figure 2. Multislice computed tomography after four cycles of panitumumab and FOLFOX4 therapy, showing the liver with several metastases, maximal diameter being 11 mm

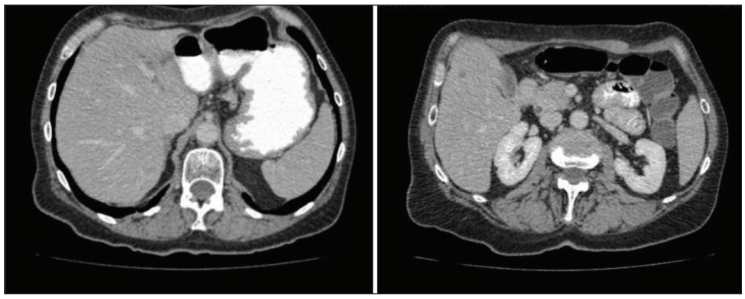


Figure 3. Multislice computed tomography after eight cycles of panitumumab and FOLFOX4 therapy, showing several liver lesions, maximal diameter being 10 mm

real-time polymerase chain reaction method did not detect mutations in exons 2, 3, and 4 of *KRAS* and *NRAS* genes in the tumor specimen.

The patient started treatment consisting of panitumumab (6 mg/kg, on the first day; biweekly) and FOLFOX4 (oxaliplatin 85 mg/m^2 on the first day; leucovorin 200 mg/m^2 on the first and second day; 5-fluorouracyl 400 mg/m^2 in bolus and 600 mg/m^2 in continuous infusion on the first and second day; biweekly). After four cycles of therapy (two months), MSCT of the abdomen showed liver with several metastases in both lobes, maximal diameter being 11 mm (Figure 2). The therapy response was estimated as partial response according to Response Evaluation in Solid Tumors (RECIST) criteria. Tumor marker CEA showed a sharp decline to 3.9 ng/ml. The patient developed rash on the face and the upper thorax, grade 2 according to Common Terminology Criteria of Adverse Events, well controlled with oral tetracycline and topical hydrocortisone treatment. After the same therapy for four more cycles, MSCT showed several liver lesions, maximal diameter being 10 mm (Figure 3); according to RECIST it was a stable disease. Tumor marker CEA was 2.2 ng/ml, and the levels of aspartate aminotransferase and alanine aminotransferase normalized.

The patient was operated on after receiving four more cycles of FOLFOX4 chemotherapy. The patient had liver operation, bisegmentectomy of S5 and S7 and metastasectomy of S3 and S4 liver segments. Four liver fragments with multiple whitish lesions, diameter ranging 2–7 mm, were microscopically analyzed. In one lesion metastatic adenocarcinoma focus was found, with 90% of surrounding necrosis. The other lesions consisted of fibrous and necrotic tissue, without vital tumor cells, proving pathological complete response (pCR).

After the surgery of liver metastases, regular follow-up was advised. At the last check up, 12 months after the surgery, the patient was without symptoms, MSCT scan was without signs of relapse, and tumor markers were in reference ranges.

The patient gave written informed consent to participate in the study, approved by the Ethics Committee of the Clinical Centre Niš and Faculty of Medicine, University of Niš. This case report has also been approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the case report.

DISCUSSION

The goal of systemic treatment in mCRC depends on the tumor burden and resectability of metastases [6]. In the case of unresectable oligometastatic disease, biological and chemotherapy should induce shrinkage of metastases to

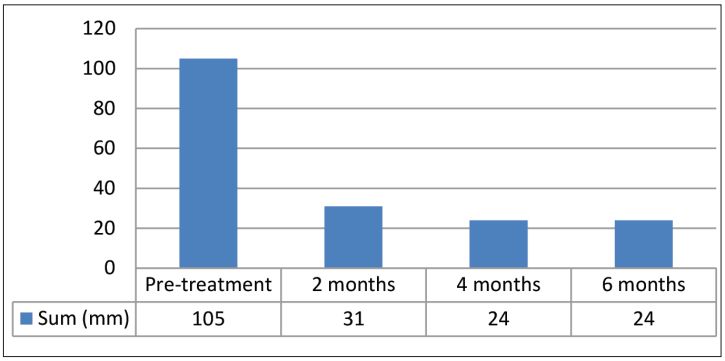


Figure 4. The sum of targeted lesions during treatment

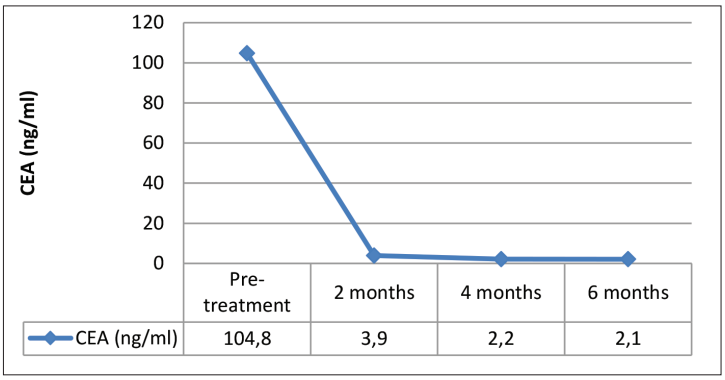


Figure 5. The level of carcinoembryonic antigen (CEA) during treatment

convert them to resectable, in order to be surgically removed. Numerous big cohort analyses have shown the benefit of surgery for liver or lung metastases, in terms of progression-free survival (PFS) and overall survival (OS) [7, 8]. A large rate of early liver recurrence after the resection of metastatic disease induced the search for prognostic and predictive factors, in order to select patients for which surgical procedure is most valuable. Reported good prognostic parameters for patients with operated colorectal liver metastases are older age, up to four metastases, metachronous disease, left-sided localization of primary tumor, and the absence of extrahepatic disease [9–12].

Conversion therapy should be the most potent one in terms of response rate and tumor shrinkage [13]. For patients whose tumors do not harbor mutations in *RAS* genes, *RAS* wild type (WT), anti-EGFR antibodies combined with chemotherapy induced better response rates and exhibited more frequent novel radiological parameters, such as early tumor shrinkage (ETS) and depth of response (DOR), compared to bevacizumab [14, 15]. The importance of ETS and DOR is even beyond conversion and resection rates, while it is proved that it correlates with survival outcomes [16, 17].

In recent years, tumor sidedness has become an important prognostic as well as predictive factor in mCRC treatment. Left colon extends from rectum to the splenic flexure, and right colon includes parts from transversal colon towards caecum. The two colon sides differ not only in embryological origin, vascular and nervous supply, main functions and microbiotic arrangement, but also in molecular mechanisms of tumorigenesis. The difference in driver mutations between the right- and left-sided CRC determines its pathologic behavior, prognosis, as well as anti-EGFR treatment efficacy [18]. A retrospective analysis of pivotal panitumumab trials showed that in patients with left-sided mCRC, panitumumab provided better outcomes, and patients with right-sided cancer did not have that benefit, in the *RAS* WT population, as well as in the *RAS*/*BRAF* WT subgroup [19, 20, 21]. A pooled analysis of six randomized trials revealed similar results, where the effect of the tumor side on the outcomes in patients treated with panitumumab or cetuximab was examined. Significant improvement in PFS and OS for patients treated with anti-EGFR antibodies was evident only for patients with left-sided mCRC, and for right-sided tumors such benefit was absent, except that the overall response rate was higher compared to bevacizumab treatment [22]. Conversely, most of the studies which examined the effect of tumor sidedness on bevacizumab treatment confirmed similar efficacy in both colon sides [23, 24]. Therefore, international guidelines for mCRC treatment suggest anti-EGFR treatment only for left-sided *RAS*/*BRAF* WT tumors, while right-sided mCRC (from caecum to hepatic flexure) should be treated with bevacizumab, irrespective of mutational status. However, the data regarding the effects of panitumumab/cetuximab in mCRC originating from transversal colon is lacking [3, 6].

We report an extraordinary effect of panitumumab and FOLFOX4 treatment in right-sided mCRC originated from transversal colon. The treatment with panitumumab and FOLFOX4 induced ETS by 70.5% (Figure 4), DOR to nearly 80% and rapid decline of CEA (Figure 5). Excellent response manifested as near total pCR, which is uncommon and very rare in mCRC treatment. The parameters such as ETS ≥ 20–30%, high DOR and pCR are linked with favorable prognosis in mCRC patients [16]. Surgery of liver metastases is also a contributing factor to better survival. Since the patient had all these positive prognostic factors, one could expect long PFS and OS.

A literature search found one similar case report of pCR in transversal colon cancer with retroperitoneal lymphadenopathy after cetuximab and FOLFOX6 treatment [25]. However, this clinical observation deserves further research in order to make definitive conclusions about transversal colon responsiveness to anti-EGFR therapy. Detailed comprehensive studies of genetic features of cancers originating from specific colon parts are needed, and hold a key to personalized treatment options and better outcomes for patients with mCRC.

ACKNOWLEDGEMENT

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Conflict of interest: None declared.

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Патолошки комплетан одговор код метастатског десностраног карцинома колона леченог панитумумабом и хемиотерапијским режимом *FOLFOX4*

Миљана Џунић[1], Ана Цветановић[1,2], Иван Петковић[1,2], Ивана Тодоровић-Стојановић[3]

[1]Универзитетски клинички центар Ниш, Клиника за онкологију, Ниш, Србија;
[2]Универзитет у Нишу, Медицински факултет, Ниш, Србија;
[3]Општа болница у Пироту, Пирот, Србија

САЖЕТАК

Увод Препоручени биолошки агенси за лечење левостраног метастатског колоректалног карцинома (мКРК) без мутација у генима *RAS*/*BRAF* јесу цетуксимаб или панитумумаб, док се за десностранi мКРК препоручује бевацизумаб. За мКРК трансверзалног колона нема података о ефикасности биолошке терапије. Приказујемо болесницу са десностраним мКРК порекла трансверзалног колона код које је третман са панитумумабом уз хемиотерапију резултовао одличним исходом.

Приказ болесника Код жене старости 56 година дијагностикован је аденокарцином трансверзалног колона, без мутација у *RAS* генима, са бројним метастазама у оба лобуса јетре. Након операције примарног тумора болесница је лечена применом панитумумаба и хемиотерапије *FOLFOX*4. После два месеца третмана евидентиран је драматичан одговор – сума дијаметара циљних лезија смањила се за 70,5%. После још два месеца терапије примећено је даље смањење за 22,5%. Накнадно су оперисане метастазе у јетри. Хистопатолошки налаз открио је фиброзно и некротично ткиво у свим сумњивим лезијама, изузев у једном фокусу, где је пронађен аденокарцином, али са околном некрозом од 90%. Дванаест месеци после хирургије јетре болесница је без прогресије болести.

Закључак Детаљно истраживање генетских карактеристика мКРК кључно је за примену персонализованих терапијских опција и бољи исход лечења болесника са мКРК.

Кључне речи: колоректални карцином; панитумумаб; трансверзални колон; метастазе у јетри