Case Reports in Oncology
Case Rep Oncol 2010;3:154–159
DOI: 10.1159/000312107
Published online: May 7, 2010

ISSN 1662–6575
www.karger.com/cro

Long-Lasting Tumor Response in Patients with Panitumumab Monotherapy for Chemorefractory Metastatic Colorectal Carcinoma – A Report of Two Cases

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Key Words
Metastatic colorectal carcinoma · Panitumumab monotherapy · Fourth-line therapy

Abstract
Background: Second as well as higher-line therapies have a significant influence on progression-free and overall survival of metastatic colorectal cancer patients. However, treatment of late-stage disease remains suboptimal. Therefore, the introduction of new, effective and well-tolerated agents is of major importance.
Case Reports: Here we describe the cases of 2 patients with metastatic *KRAS* wild-type colorectal cancer who received a fourth-line monotherapy with panitumumab after failure of 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab.
Results: Both patients achieved a partial remission, and for 11.5 and 18 months, respectively, they had a stable disease with initial reduction in the tumor marker carcinoembryonic antigen. Both patients reported a good tolerability of the treatment with improved quality of life (compared to receiving combined chemotherapy).
Conclusion: Panitumumab monotherapy is an effective and well tolerated treatment of metastatic colorectal cancer in extensively pretreated *KRAS* wild-type patients. Our data have shown a response to panitumumab monotherapy for more than 11 months.

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Introduction

During the previous 10 years, a significant improvement has been observed in the treatment of metastatic colorectal cancer patients, which is largely due to the introduction of new cytotoxic drugs (irinotecan, oxaliplatin) and targeted therapies (bevacizumab, cetuximab, panitumumab). As therapeutic options expanded, overall survival improved incrementally from a median of approximately 12 months (achievable with 5-fluorouracil/folinic acid monotherapy) [1] to more than 20 months in patients who are given 2 or more effective drugs in combination or sequentially [2, 3]. It has become increasingly clear that combination therapy is effective in treating advanced disease [4–6]. However, in cases with progression under modern chemotherapy, the development and introduction of new effective agents is of major importance. This is especially true for agents like the approved epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab that have demonstrated efficacy in the management of late-stage disease.

Panitumumab is the first fully human anti-EGFR monoclonal antibody and is a very promising new treatment option for patients with *KRAS* wild-type metastatic colorectal carcinoma. The efficacy of panitumumab monotherapy has been demonstrated in the pivotal open label phase III study [7, 8] in which panitumumab significantly prolonged progression-free survival versus best supportive care in patients with wild-type *KRAS* tumors refractory to standard chemotherapeutic agents.

Here we present two patients who benefited from fourth-line treatment with panitumumab.

Case Reports

Case 1

A 68-year-old man with good performance status was diagnosed with a tumor in the colon sigmoideum (June 2006). Thoracic CT-scan revealed lung-metastases, and PET-scan suggested additional liver metastases. While the primary sigmoid tumor was left in situ, first-line treatment with FOLFIRI/bevacizumab was initiated in July 2006 and pursued until July 2007. Meanwhile, the treatment was interrupted three times on the patient's request to regain a quality of life without chemotherapy. In July 2007, the treatment was switched to second-line therapy with FOLFOX because of local tumor progression.

In February 2008, third-line treatment with FOLFIRI was introduced and terminated in May 2008 as a result of side effects such as nausea, vomiting, loss of appetite and general weakness. After wild-type *KRAS* tumor status was confirmed, monotherapy with panitumumab (6 mg/kg every 2 weeks) was initiated (June 2008) and administered for 23 cycles (until May 2009). Treatment with panitumumab resulted in a good partial response of the primary tumor (**fig. 1**). Concomitantly, a decline of the carcinoembryonic antigen (CEA) serum levels to normal was observed from 7.6 µg/l in July 2008 to 3.4 µg/l in March 2009 (normal values ≤3.4 µg/l) (**fig. 2**). The size of the lung metastases had not changed significantly until then. However, from April 2009, CEA-values increased successively to 5.0 µg/l, and follow-up staging resulted in a size increase of the oligotope lung metastases (index metastasis from 1.6 × 2.5 cm to 2.6 × 3.4 cm) leading to the re-introduction of FOLFIRI as combination therapy with panitumumab in May 2009 for another 6 cycles, when FOLFIRI was continued without the antibody.

Tolerability of panitumumab monotherapy proved to be very good, the quality of life improved and the patient gained weight (5 kg). The patient experienced neither emesis nor vomiting and did no longer suffer from oxaliplatin-induced neuropathy. The only treatment-related side effect was skin toxicity (WHO grade 2), which was treated with a greasy ointment containing paraffinum liquidum and glycerin and a nadifloxacin-containing anti-acne ointment. Under panitumumab monotherapy, the patient had regained his quality of life with an improvement of the Karnofsky index from initially 70–

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80% to now 100%. The patient is up to now (04/2010) in a good health state and continues to receive combination therapy.

Case 2

A male patient aged 79 years was diagnosed in October 2003 with an adenocarcinoma of the rectum, massive lymphangiosis carcinomatosa, and infiltration of regional lymph nodes (stage IIIC). Between December 2003 and May 2005 the patient was treated with deep anterior resection of the rectum (R0) and received adjuvant chemoradiation with 5-fluorouracil/folinic acid. In August 2005, new lymphogenic infiltration and metastases in the lung were diagnosed. First-line treatment with 5-fluorouracil/folinic acid and bevacizumab was initiated and pursued until June 2006 when chest X-ray and abdominal CT revealed pulmonary progression. Second-line treatment with FOLFOX was started in October 2006 and terminated in May 2007 as a result of renewed progression (abdominal CT and ultrasound). From July 2007 the patient received third-line treatment with FOLFIRI. In January 2008, a metastasis of the liver was detected by CT-scan, which was shown to be *KRAS* wild-type by biomarker testing on metastasis material after fine-needle biopsy. In February 2008, panitumumab monotherapy (6 mg/kg every 2 weeks, with one interruption) was initiated which resulted (August 2008) in a decrease of lymphatic lesions, in particular in a reduction of the beforehand enlarged abdominal lymph nodes, as well as a partial remission of the liver metastases (**fig. 3**). In addition, a reduction in CEA levels from 369.0 μg/l (February 2008) to 108.7 μg/l (August 2008) was observed. In January 2009 CEA levels had risen to 283.3 μg/l. The lung metastases remained unchanged.

Treatment with panitumumab was very well tolerated, with mild skin reactions (grade 1) which were treated with a metronidazole-containing cream. After 34 cycles of panitumumab monotherapy, the treatment was again changed to combination therapy. The patient has a stable partial remission and stays continuously under treatment. The patient has unremarkable liver counts and does not suffer from hematological toxicity. Due to the very good efficacy and tolerability of the therapy, the patient now still has a high quality of life.

Discussion

Both our patients had visceral metastases and failed prior treatment with 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab. In spite of extensive pretreatment, stable disease was observed after switching treatment to panitumumab monotherapy for 11.5 and 18 months, respectively, when combination therapy was re-introduced in both patients. These progression-free intervals are remarkably good for patients who receive a fourth-line therapy. Both patients benefited from good tolerability of the treatment and an improved quality of life. The good experience with panitumumab treatment in these 2 heavily pretreated patients is in line with the results of the pivotal studies [7, 8].

The EGFR inhibitors cetuximab and panitumumab were found to be significantly superior over best supportive care in randomized trials when given to patients who had already received two or more lines of chemotherapy [7, 9]. However, the real potential of EGFR inhibitors was not fully recognized until *KRAS*-mutation status was confirmed as a predictive marker [8]. A subgroup analysis of the pivotal study showed [8] that patients with wild-type *KRAS* tumors refractory to standard chemotherapy achieved a marked and significant prolongation of progression-free survival when treated with panitumumab as compared with best supportive care (median 12.3 vs. 7.3 months, $p < 0.0001$). Disease control was also improved with 51% versus 12% benefiting from treatment (PR, SD). Furthermore, panitumumab proved to be safe and well tolerated. In the pivotal trial less than 2% of patients had potential infusion reactions (grade 3 in 0.1% of patients) [10]. The main treatment-related toxicity was skin related (≤5% grade 3) and consisted of erythema, acneiform dermatitis or pruritus. Recent evidence suggests that prophylactic

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treatment may reduce the incidence of treatment-related skin toxicity by more than 50% [11].

The optimal use of panitumumab in the treatment of metastatic colorectal cancer is yet to be determined. Currently, combinations of panitumumab with standard chemotherapies are being evaluated as first or second-line strategies in phase III randomized clinical studies. Based on currently available data and our current experience, it can be concluded that panitumumab is an effective and well tolerated monotherapy of metastatic colorectal cancer even in extensively pretreated patients. Moreover, panitumumab treatment may allow to bridge treatment breaks when chemotherapy has to be temporarily interrupted because of side effects.

Acknowledgements

Financial support for medical writing was provided by Amgen Germany. Both patients gave their written informed consent for the publication of this article.

Fig. 1. Colonoscopic images of the primary carcinoma of the colon sigmoideum (case 1). **a** Before starting therapy with panitumumab; **b** after 12 cycles; **c** after 23 cycles.

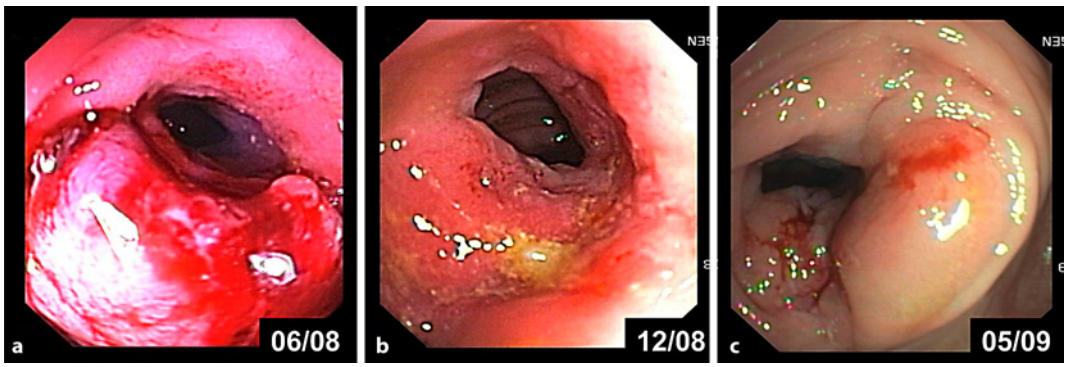

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Fig. 2. Serum CEA levels during fourth-line treatment with panitumumab (case 1).

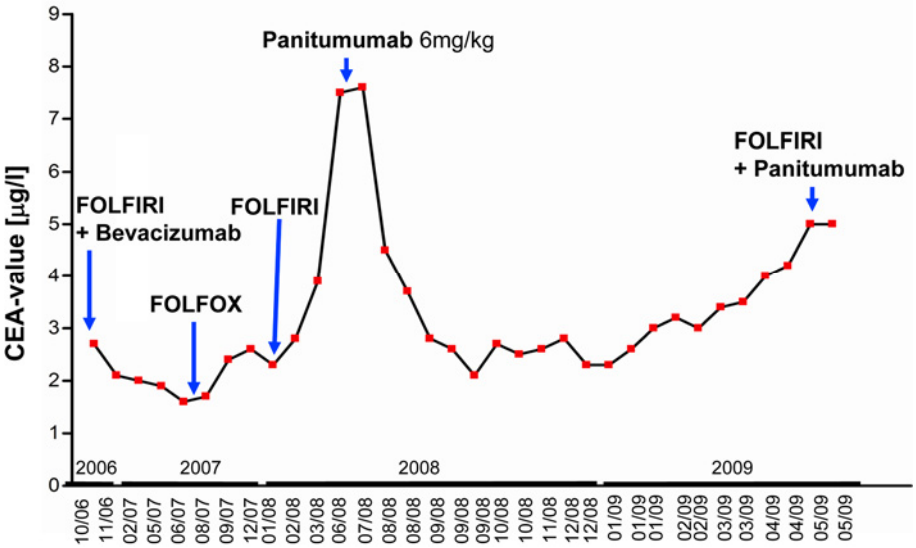
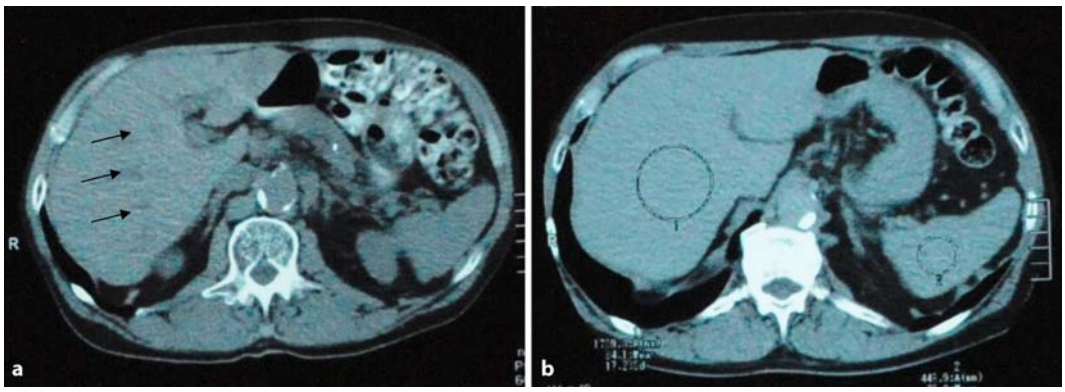


Fig. 3. CT scans of liver metastases in a patient with an adenocarcinoma of the rectum: **a** at diagnosis of the metastases (January 2008) and **b** after 6 months (August 2008) of fourth-line treament with panitumumab (case 2).



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