Case report: impressive response to pembrolizumab in a patient with mismatch-repair deficient metastasized colorectal cancer and bulky disease

Markus Kieler, Werner Scheithauer, Christoph C Zielinski, Andreas Chott, Ali Al-Mukhtar, Gerald W Prager

Abstract
Here, we report the history of a 42-year-old female patient with sporadic mismatch-repair-deficient metastatic colorectal cancer and abdominal bulky disease, who received pembrolizumab (200 mg every 3 weeks) after the failure of third-line treatment. Restaging 3 months after initiation of treatment revealed a striking response with shrinkage of the bulky peritoneal tumour mass (baseline size 11×11×14 cm) to nearly 25% of the original tumour volume (6.2×7.1×10.4 cm). Restaging 8 months after initiation showed further downsizing of the tumour mass (5.5×7.0×8.0 cm). Tumour markers CEA and CA 19-9 decreased to normal levels, haemoglobin level increased from 8 to 13 mg/dL and her overall clinical performance status increased from ECOG 3 to 1 within 3 months. Therapy with pembrolizumab was continued and is still ongoing. We emphasise the importance of testing for mismatch-repair status in metastatic disease.

Background
Colorectal cancer (CRC) is the second most frequent cancer diagnosed in Europe with an incidence about 447,000 new cases per year. Approximately 25% of patients present with metastases at the time of initial diagnosis and nearly 50% of patients will develop metastases, contributing to the high mortality rates reported for CRC. The CRC-5-years survival rate in Austria is about 65%. As there are novel therapeutic options now available for a subset of patients with mCRC, the microsatellite instability status should be assessed at the time of diagnosis. Immunotherapy with checkpoint inhibitors might also be a therapeutic option in mCRC patients with bad performance status, not capable of receiving standard chemotherapy.

Key questions

What is already known about this subject?
Immunotherapy with checkpoint inhibitors has proven to yield remarkable responses in a variety of malignancies. It has been shown that in colorectal cancer (CRC), tumours with mismatch-repair-deficiency are especially susceptible to blockade with antibodies targeting PD-1 or PDL-1.

What does this study add?
To the best of our knowledge, this is the first report of a patient with a very large bulky tumour mass from her relapsing CRC that responded to PD-1-blockade with pembrolizumab after progressing under standard chemotherapy and bad performance status (ECOG 3) at initiation of therapy.

How might this impact on clinical practice?
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repeated DNA motifs (microsatellites), is typically caused by epigenetic silencing or mutation of DNA mismatch repair genes. The suggested approach to evaluate MSI is via PCR of five DNA markers or immunohistochemical analysis of DNA mismatch repair enzymes. Immunostaining of the mismatch repair enzymes MLH1, MSH2, MSH6 and PMS2 is equivalent in levels of sensitivity and specificity to MSI analysis via PCR. In our centre, a two-step approach is performed. If the immunohistochemistry is negative for one of the above-mentioned mismatch repair enzymes, the suspected MSI is confirmed via PCR.

The microenvironment of microsatellite instable colon cancer displays high infiltration with activated CD8+ CTL as well as activated Th1 cells. It has been shown that MSI tumours counterbalance this active Th1/CTL microenvironment by expression of multiple immune checkpoints such as programmed death 1 (PD-1). The binding of PD-L1 or PD-L2 to PD-1 results in inhibition of T-cell immune functions and can constitute a form of immune escape mechanism.

In contrast to other tumours such as melanoma, renal or lung cancer, where PD-L1 is expressed by tumour cells, in MSI CRC PD-L1 is expressed predominantly by infiltrating myeloid cells.

Advances in immunotherapy, especially blocking the negative feedback pathway of PD-1 with monoclonal antibodies, have shown remarkable clinical responses in patients with different types of cancers such as melanoma, non-small-cell-lung cancer, renal cell cancer, bladder cancer and Hodgkin’s lymphoma. In May 2015, Le et al. demonstrated the clinical activity of pembrolizumab, a humanised monoclonal anti PD-1 antibody of the IgG4 κ isotype blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, on treatment-refractory progressive mCRC with mismatch-repair deficiency. In this study, a small group of patients (n=10) with mismatch-repair-deficient CRC had a partial response in 40% and a stable disease at week 12 in 50%. In contrast, patients with mismatch-repair-proficient tumours did not respond to immunotherapy and pembrolizumab was almost ineffective. These stimulating results suggest a new therapeutic option in a carefully selected subset of patients with mCRC.

**CASE REPORT**

Here, we report the history of a 42-year-old woman, who was diagnosed with stage III KRAS mutant (G13D) CRC.
in 2013, when she underwent an emergency sigma resection due to perforation. She received adjuvant treatment with eight cycles of XELOX until January 2014. In December 2014, peritoneal metastases were detected and her overall physical status decreased steadily over time. Only five cycles of FOLFIRI were administered until September 2015. Suspected disease progression was confirmed when she was restaged, showing a large unresectable bulky peritoneal metastasis with about 11×11×14 cm holding in size (baseline size 11×11×14 cm, see figures 1 and 2). When she was referred to our department in September 2015, she was incapable to walk with a reduced performance status of ECOG 3. A molecular profile of the tumour revealed mismatch-repair deficiency of MLH1/PMS2 in the tumour DNA, but not in the germline DNA. In retrospect, the tumour showed a characteristic histological picture of a high number of tumour-infiltrating lymphocytes (see figure 3). Hence, therapy with pembrolizumab (200 mg every 3 weeks) was initiated in the end of September 2015. After three cycles, a restaging was performed. No new metastases were diagnosed and com-
pared to the last scan she had a stable disease mass. After these very promising results, the treatment with pembrolizumab for another three cycles were continued. At the end of December, a CT scan showed an impressive response with shrinkage of the peritoneal tumour mass to 25% of the original tumour volume (6.2×7.1×10.4 cm, see figures 4 and 5). Tumour markers CEA and CA 19-9 and LDH levels decreased to normal levels, haemoglobin level increased from 8 to 13 mg/dL and her overall clinical performance status increased from ECOG 3 to 1 within 3 months (see figures 6–8). Restaging after 11 cycles of pembrolizumab showed further downsizing of the tumour mass (5.5×7.0×8.0 cm, see figures 9 and 10). The therapy with pembrolizumab is still ongoing.

**DISCUSSION**

While it has been proven that immunotherapy with checkpoint inhibitors may be a potent new therapeutic option in certain malignancies such as metastatic melanoma, so far in only a small sample size of patients with mCRC pembrolizumab had been tested. To the best of our knowledge, this is the first report of a sporadic MSI tumour, which responded after the failure of oxaliplatin, irinotecan and fluoropyrimidine, leading to a substantial response for at least 8 months and is ongoing. As demonstrated in previous publications and as we have also shown here, immunotherapy can yield remarkable responses in the subset of mismatch-repair-deficient colon cancer. For this reason, we emphasise the importance of testing for mismatch-repair status in metastatic disease.
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