CASE REPORT

Re-treatment Using Cetuximab and Chemotherapy in Patients with Metastatic Colorectal Cancer Harboring Wild-type RAS Gene

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Abstract: Colorectal cancer is a heterogeneous disease. Activating mutations in genes like K-RAS, BRAF, and PI3K contribute towards a poor prognosis of the disease. In this report, we present the case of re-treatment of a 58-year old patient of metastatic colorectal cancer with a combination of anti-EGFR and chemotherapy. The patient who harbored wild-type RAS gene was administered several lines of therapies including anti-EGFR antibodies. In spite of the different regimens involved, a significant progression of disease involving metastasis to the lungs and the brain was observed. On re-treatment with cetuximab and chemotherapy, the quality of life improved and the tumor biomarkers decreased. Re-treatment with anti-EGFR antibodies and chemotherapeutic agents can be an option for patients showing adverse prognosis after several lines of therapies.

Keywords: Metastatic colorectal cancer; anti-EGFR antibodies; cetuximab; K-RAS; chemotherapy

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1. Introduction

Colorectal cancer (CRC) is one of the leading causes of death among cancer patients. CRC is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidences. It is the third most common cancer worldwide and the fourth most common cause of death[1-3]. It is a heterogeneous disease, characterized by diversions in multiple molecular pathways throughout its evolutionary process[4]. In routine practice, testing of clinical samples for mutations in RAS and RAF oncogenes and for deficient DNA mismatch repair (dMMR), serves as a prognostic or predictive biomarker that provides information for patient risk stratification and assists in the choice of appropriate therapy. A mutation in the RAS gene has been reported in nearly 50% of patients with CRC across different geographical areas. Data emerging from literature clearly point out that the activating mutations of K-RAS, BRAF, and PI3K predict lack of response to anti-EGFR therapy[5,6]. Reports show that in patients with CRC, the KRAS mutations could be detected from primary tumors as well as metastatic tumors with a high rate of concordance[7]. Anti-EGFR therapy improved the relapse rate (RR) and progression-free survival (PFS) in cohorts with wild-type KRAS[8]. The third- or later-line of therapy often yields a poor survival benefit in patients with metastatic colorectal cancer (mCRC). In some patients who have developed resistance to first-line chemotherapy and anti-EGFR, but harbor the wild type RAS and BRAF, re-challenge with a combination of cetuximab and irinotecan has shown positive results. After the failure of an irinotecan-based first-line therapy in mCRC patients with wild type RAS gene, recourse to a cetuximab-based regimen could lead to the destruction of WT cells and to the prevalence of mutated clones, which leads to an initial progression of the disease. Subsequent therapy
without cetuximab could restore RAS WT clones, which constituted a major part of the tumor mass at the time of the ensuing progression of the disease. Further treatment is limited due to side effects and the lack of efficacy. The dMMR is rare in mCRC. Besides, only 3.5%-5.0% of mCRC patients may benefit from programmed cell death protein-1 (PD-1) blockade while the absolute survival benefits from tyrosine kinase inhibitors and TAS-102 is very limited. These recommended regimens are costly and not all patients can afford them. Hence, re-challenge with a combination of cetuximab and the chemotherapy in case of patients with wild type RAS and BRAF or oxaliplatin-based chemotherapy regardless of the RAS status should be considered.

2. Case Report

A 58-year old woman from a good socioeconomic status, married with children, non-smoker, no history of ethanol consumption; presented in October 2016, with a history of painless rectal bleeding and intermittent bloating for the past 2 years. She was under regular medication for hypothyroidism and hyperlipidemia. She did not suffer from anorexia, weight loss, diarrhea, constipation, a decrease in stool caliber, nausea, vomiting, or fever. She had no previous history of surgery, and had her menopause 5 years ago. She had a familial history of cancer, with her father succumbing to renal cancer at the age of 63; and sister to ovarian cancer at the age of 52. She did not have a familial history of colorectal cancer or inflammatory bowel disease.

Physical examination showed no abdominal distension, scar, mass or hernia bulge; and the rectal examination was normal. The level of carcinoembryonic antigen (CEA) was 11.1 ng/L, while all other laboratory parameters were normal.

Colonoscopy (Figure 1) revealed a lesion in the left upper rectal region and biopsy of the sample showed moderately differentiated invasive adenocarcinoma.

Figure 1. Colonoscopy pictures

Magnetic resonance imaging (MRI) of the pelvic region (Figure 2) showed a mid-rectal tumor of 7cm in circumferential (CRM) dimension T3 tumor) extending to meso-rectal fat and more than 7 lymph nodes (N2b), with extramural venous invasions (EMVI). The tumor could be classified as T3 N2b Mx tumor, Stage IIIc, EMVI positive.

Figure 2. MRI of the pelvic region sagittal and axial view

In February 2017, the patient travelled to Mayo Clinic in USA, and was started on chemoradiotherapy with oral administration of Capecitabine 1500 mg twice daily with concurrent radiotherapy for 6 weeks. On April 2017, the patient was advised FOLFOX 6 as the disease had progressed to the lungs, as seen on the CT scan and tumor markers. CT scan and tumor markers. In spite of receiving 6 cycles of FOLFOX6, the progression of the disease could not be contained. Hence, the patient was treated using a combination of FOLFIRI and Bevacizumab since July 2017. An evaluation of disease progression using biomarkers and CT scan performed in September 2017 showed metastasis in the lungs. Molecular analysis on the initial specimen of rectal biopsy showed that the patient had wild type \textit{KRAS}, \textit{NRAS} and \textit{BRAF} genes, was MMR proficient and HER2/neu negative. Though the patient showed a response after 5 cycles of treatment regimen involving FOLFIRI and Panitumumab, after additional 2 cycles an evaluation of the disease status using CT scan was done in January 2018; the chest X-ray showed significant right side pleural effusion (Figure 3) and had increased biomarkers (Figure 4) indicating a significant progression of the disease. The pleural effusion was drained continuously using a drainage chest tube. Further treatment was planned with regorafenib and immunotherapeutic agents, but the patient preferred to return to her country.

Figure 3. Chest X-ray
CEA: carcinoembryonic antigen

She returned to Qatar in January 2018, and was started on orally administered one cycle of regorafenib 120 mg daily for a period of three weeks. However, this regimen was discontinued due to issues related to drug intolerance and disease progression. She suffered from a further increase in tumor biomarkers and pleural effusion that had to be drained out continuously at the NCCCR facility, Doha, Qatar.

In March 2018, although no RAS testing was performed again, the patient was treated again with chemotherapy (FOLFOX6) and cetuximab every 2 weeks. After 4 cycles of this regimen, the accumulation of pleural effusion stopped (Figure 5) without any pleurodesis, the drainage tube was removed and a significant drop in biomarker was observed (Figure 6) from 5000 ug/L to 800 ug/L, all these indicating a good response to treatment.

3. Discussion

Studies have shown that in case of a failure of irinotecan-based first-line therapy, re-treatment with cetuximab regimen destroyed the wild type cells and the disease progressed due to the prevalence of mutated clones[10]. A further line of therapy without cetuximab restored the RAS WT clones, which constituted a major part of the tumor mass as the disease progressed[11]. Here, we report a case of a CRC patient with wild type RAS gene showing disease progression with first and second line treatment which included anti-EGFR antibodies, but responded to re-treatment with FOLFOX6 and Cetuximab which was
evident by clinical improvement and stoppage of pleural effusion accumulation with out pleurodesis and removal of the chest tube, clear improvement in the chest X-ray with significant drop in the CEA from 5000 ug/L to 800 ug/L. So with re-treatment, it was seen that the quality of life of the patient improved for a period of 6 months before the health of the patient finally deteriorated. Several studies, including the CRICKET trial, report the enrolment of mCRC patients with wild-type RAS and BRAF at baseline. All patients received first-line treatment with cetuximab and irinotecan-containing regimens and demonstrated at least a partial response (PR) when analyzed using RECIST criteria. After progression-free survival of at least 6 months, the disease progressed within 4 weeks of the last dose of cetuximab. These patients received a combination of oxaliplatin and bevacizumab as second-line therapy. Following a second progression, the patients received cetuximab and irinotecan until the disease worsened. The response rate was measured as the primary endpoint.[12]

Another common practice is re-treatment using oxaliplatin-containing regimens as the third or later-line of therapy, though the evidence is limited. A study by Yang et al. showed that re-challenge using oxaliplatin-containing regimens resulted in tumor control and survival benefit equivalent to that of treatment with anti-EGFR antibodies and irinotecan in mCRC.[13]

As observed from this case study, re-treatment with anti-EGFR antibodies and oxaliplatin containing regimens are options for mCRC patients with wild type all RAS and BRAF genes in case of disease progression after several lines of treatment. However, this concept requires further evaluation as part of a randomized trial.

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