Case report

Efficacy of trifluridine/tipiracil as IV line chemotherapy in a young woman with metastatic colorectal cancer. A case report

Rafał Wiśniowski

Department of Oncology and Hematology,
Beskid Oncology Centre – John Paul II Memorial City Hospital in Bielsko-Biala

Correspondence:
Rafał Wiśniowski
Department of Oncology and Hematology,
Beskid Oncology Centre – John Paul II
Memorial City Hospital in Bielsko-Biala
43-300 Bielsko-Biała, ul. Wyzwolenia 18
phone: 33 498 40 00

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ABSTRACT

Colorectal cancer is the most common gastrointestinal malignancy and the third most frequently diagnosed cancer worldwide. Trifluridine/tipiracil represents an approved option for the treatment of advanced metastatic colorectal cancer in patients who are refractory, or are not considered candidates for currently available therapies. We present a case of a young woman with refractory metastatic colorectal cancer treated with this agent as the IV line of chemotherapy in which remarkable prolongation of progression free survival time was observed.

Key words: metastatic colorectal cancer, chemotherapy, trifluridine/tipiracil, progression free survival

INTRODUCTION

Colorectal cancer (CRC) is the most common gastrointestinal malignancy and the third most frequently diagnosed cancer worldwide. The incidence of CRC is increasing in Asia and Eastern Europe, mostly due to the risk factor increase (unhealthy diet, obesity and smoking) [1]. Approximately 25% of CRC patients present metastases at initial diagnosis, while almost 50% will develop this fatal complication in the course of the disease [2].

The therapeutic armamentarium of mCRC consists of a continuum of care including a sequence of combination chemotherapy regimens (including 5-fluorouracil, irinotecan and oxaliplatin) associated with biological targeted agents such as anti-vascular endothelial growth factor (VEGF) monoclonal antibodies – e.g. bevacizumab, and anti-epidermal growth factor receptor (EGFR) monoclonal antibodies – e.g. cetuximab [3].

Current treatment regimens notably prolonged the median survival time of patients with mCRC. In recent clinical trials, the median overall survival (OS) from I line therapy in mCRC has reached approximately 30 months. Nevertheless additional treatment options for mCRC patients who have progressed on multiple therapies represent a significant unmet need [4].

Trifluridine/tipiracil (FTD/TPI) is a novel orally administered antineoplasmatic thymidine-based nucleoside analog which represents an approved option for the treatment of advanced metastatic CRC (mCRC) in patients who are refractory, or are not considered candidates for currently available therapies [5].

Trifluridine (FTD) which inhibits thymidylate synthase is the active cytotoxic component of the FTD/TPI, while TPI improves the bioavailability of the latter. Additional antineoplasmatic activity of FTD/TPI which distinguishes it from traditional fluoropyrimidines results from trifluridine incorporation into DNA which finally leads to double-helical DNA damage [6].

The efficacy of FTD/TPI in the treatment of the refractory mCRC has been confirmed in the randomized phase III clinical trial RECOURSE. Therapy with FTD/TPI, significantly prolonged median overall survival (OS) and progression free survival (PFS), improved disease control rate and extended median time to deterioration of performance status compared to placebo [7].

We present a case of a young woman with refractory mCRC treated with FTD/TPI as the IV line of chemotherapy in which remarkable prolongation of progression free survival time was observed.

CASE REPORT

A 26-year-old patient with no history of chronic diseases and no treatment used before, in November 2014, underwent sigmoid cancer right hemicolectomy due to intestinal obstruction. During the procedure, the sigmoid tumor was removed with surgical margin. Histopathological findings revealed: adenocarcinoma invasivum tumor G2. The staging was assessed at pT3N1Mx (one metastatic nodules in 32 examined lymph nodes). Computed tomography performed prior to systemic treatment did not reveal dissemination of neoplastic disease.

After that the patient was qualified for chemotherapy FOLFOX4 (oxaliplatin, fluorouracil). She received 10 infusions planned over a 6-month period of treatment, December 2014 – June 2015 complicated periodically by grade II neutropenia.

In June 2015, CT of the abdomen, pelvis and thorax was performed followed by abdominal MRI, in which hepatic metastasis was found in the 4a segment 10 ×11 mm. PET/CT – without other dissemination; CEA was 43.1 ng/mL

It was decided to perform metastasectomy of the lesion at the General, Transplant and Liver Surgery Clinic in Warsaw. The procedure was performed in September 2015. The lesion in segment 4a and a single cancer implant in the peritoneum (HP: adenoca metastaticum) were removed.

Due to the short history, it was decided to include II line chemotherapy with FOLFIRI (irinotecan, fluorouracil). In the meantime, treatment was switched to XELIRI (at the patient's request). The treatment was complicated by hematological toxicity (CTC II neutropenia and CTC II thrombocytopenia) – prednisone induction was used with good results. In total, patient received 6 months of therapy with hematological complications (from October 2015 to April 2016).

In May 2016 CT suggested of cysts of ovaries to 5.5 cm. Mutually. After discussing with the patient, it was decided to refer the patient to the Gastrointestinal Surgery Clinic of the Medical University in Lublin for HIPEC (*Hyperthermic Intra-Peritoneal Chemotherapy*). This procedure was performed on June 2016 with removal of the reproductive organ and peritoneal lesions (HP: adenocarcinoma metastaticum).

Due to the HIPEC procedure, the patient was referred again for CT examination (PET/CT was considered as non-diagnostic due to the above-mentioned therapy). In July 2016 CT suggested of the lesion in the area of IVC d. 23 × 12 mm at the level of the orig-

ination of common iliac vessels; CEA 2.2 ng/mL. In September 2016 PET/CT dissemination to the retroperitoneal lymph nodes as in CT; CEA 4.6 ng/mL. After discussing with the patient, it was decided to attempt stereotactic radiotherapy of lesions near the aorta at the UCK Oncology Clinic in Katowice.

Stereotactic radiotherapy was performed in November 2016.

After 4 months of observation, the CEA marker increased again to 7.2 ng/mL (March 2017), and in CT the features of pulmonary dissemination and progression in retroperitoneal cavity occured. After excluding mutations in the KRAS, NRAS and BRAF genes in histopathological specimen, it was decided to start palliative therapy with cetuximab in line III. The CEA marker was 7.2 ng/mL. Treatment was carried out with a scheme of every 7 days from March 2017 to October 2017. Treatment was tolerated well.

In October 2017, the CEA marker again (sensitivity of the test positive for the patient) increased from 7.2 ng/mL in March 2017 to 18.4 ng/mL. In addition, in CT there were progression features according to RECIST. It was decided to include TAS-102 in therapy. She received a dose of 2 × 50 mg on days 1st–5th and 8th–12th on a 28-day cycle.

Already during TAS-102 therapy, neutropenia in CTC II grade and a slow increase in the CEA marker from 80 to 132 ng/mL were observed, without progression in imaging studies. Patient reported CTC weakness as the main ailment. The second course was given with a week delay after obtaining an increase in neutrophilia. It was recommended to include prednisone 20 mg 3 days before the next chemotherapy course in order to improve bone marrow function parameters.

After 3 and 6 months of treatment, computed tomography of the chest and abdominal cavity with pelvis was performed, where the stabilization was found according to the RECIST scale.

In the subsequent months of therapy, the patient reported increasing fatigue, which interfered with her daily duties, the patient's general condition was assessed at WHO 1.

In another tomographic examination performed on June 2018 (before the sixth course), progression of changes compared to the previous study was found. TAS-102 intake was withheld. Due to the patient's relatively good general condition, but periodic depression, it was proposed to include another chemotherapy line – mitomycin/capecitabine. The patient received treatment in the above-mentioned schedule, from December 2018 to February 2019 she obtained a significant regression of the CEA marker after just one month of treatment, however, due to clinical progression (obstruction), therapy was stopped and the patient was referred for further symptomatic treatment at Home Hospice.

DISCUSSION

According to the current guidelines of European Society for Medical Oncology (ESMO) and the statement of the European Medicines Agency (EMA) trifluridine/tipiracil is the oral agent approved in the palliative setting for the treatment of mCRC in patients who are refractory, or are not considered candidates for currently available therapies [5, 8].

The basis for introducing the FTD/TPI to the current oncological guidelines were the spectacular results of the RECOURSE clinical trial published in "New England Journal of Medicine" in 2015. All patients were pretreated with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and – for patients with KRAS wild-type tumors – with cetuximab or panitumumab. Furthermore, about 60% of patients in both arms received four or more therapeutic regimens prior to randomization.

In the RECOURSE trial therapy with FTD/TPI, significantly prolonged median overall survival (OS) compared to placebo (7.1 vs. 5.3 months; hazard ratio (HR) 0.68; $p < 0.0001$). In addition, FTD/TPI significantly prolonged median progression free survival (PFS); 2.0 vs. 1.7 months; HR = 0.48; $p < 0.0001$), improved disease control rate and extended median time to deterioration of performance status compared to placebo. The most common adverse events during treatment with FTD/TPI were haematological and gastrointestinal and were observed more often during the first dosing cycle of the studied drug. The main dose-limiting toxicity in RECOURSE was neutropenia observed in 66% of patients. There was no difference between the two groups in the development of stomatitis, hand-foot syndrome, or cardiac events.

Our case concerned a "typical" patient with mCRC qualified for the RECOURSE study, i.e. not eligible or refractory for currently available therapies. Despite the significant advancement of the neoplastic process, the therapy with FTD/TPI was well tolerated for a long time and the side effects were controlled without major clinical problems.

Considering the median PFS difference between FTD/TPI and placebo of 0.3 months reported in RECOURSE trial, the absolute 8 months PFS observed in our patient is clinically meaningful.

CONCLUSION

Our clinical observation confirms that FTD/TPI can be considered as a new valid option for chemotherapy in mCRC patients who have exhausted any chance of treatment. At the same time, it confirms the importance of the continuum of care in the treatment strategy of mCRC.

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