

Case Report

# Beneficial Treatment Management with Trifluridine/Tipiracil in a Patient with Metastatic Colorectal Cancer and Pronounced Hematological Event History during Previous Treatments

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## Keywords

Colorectal cancer · Chemotherapy · Trifluridine/tipiracil · Dose reduction · Myelosuppression · Granulocyte colony-stimulating factor · Hemotoxicity

## Abstract

Trifluridine/tipiracil (FTD/TPI) significantly improves overall survival in patients with metastatic colorectal cancer (mCRC). The most common treatment-related event (grade  $\geq 3$ ) was hematological toxicity. We here report long-term disease-stabilizing FTD/TPI treatment of an mCRC patient (KRAS wild-type, ECOG performance status 1 at baseline and at the end of FTD/TPI therapy) with multifocal synchronous metastases and a longstanding history of extensive hematological events during previous treatments. Finally, this 62-year-old male patient was treated for 10 months with FTD/TPI by consecutive alteration of treatment parameters: (i) initial daily dose reduction to 80 mg (72% of the recommended dose), (ii) 20 days

dose delay, (iii) a second and later third dose reduction to 70 mg and 60 mg (about 64% and 55%, respectively, of the recommended dose), and (iv) 30 µg per day of granulocyte colony-stimulating factor administration first for 3 days, and later for 5 days, for each treatment cycle.

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## Introduction

Trifluridine/tipiracil (Lonsurf®, TAS-102), an oral antineoplastic nucleoside analog, represents an approved option for the treatment of advanced metastatic colorectal cancer (mCRC) in patients who are refractory to, or are not considered candidates for, currently available therapies. Trifluridine (FTD) is incorporated into DNA, thus finally leading to double-helical DNA breakages. Tipiracil (TPI) increases FTD's efficacy by maintaining the FTD blood concentration by inhibiting the thymidine phosphorylase responsible for FTD degradation [1, 2]. In the pivotal phase III trial RECURSE, the median overall survival improved from 5.2 months with best supportive care plus placebo to 7.2 months with FTD/TPI at the final data cut in October 8, 2014 (hazard ratio 0.69, 95% confidence interval, 0.59–0.81;  $p < 0.001$ ) [3–5]. The most common treatment-related serious adverse events of grades 3 and 4 were hematological, e.g., leukopenia, neutropenia, anemia, or thrombocytopenia that occurred in 21, 38, 18, or 5% of the 533 mCRC patients receiving FTD/TPI [3]. Due to this hematotoxicity profile, it remains a great challenge for physicians to transfer the FTD/TPI administration into clinical settings with mCRC patients that had already had manifestations of serious hematological events along their treatment history. In this report, we present an mCRC case in which these hematological events could be managed successfully by means of dose reduction and treatment delay as well as preventive granulocyte colony-stimulating factor (G-CSF) administration [6, 7].

## Case Report

A 62-year-old male patient was referred to our clinic with advanced mCRC showing synchronous lung and liver metastases in September 2009. During the first colorectal surgery of the synchronous carcinoma of the proximal rectum and the sigmoid colon (each pT3), 2 of 16 resected lymph nodes were found to carry cancer cells (pN1). At the resection margin of the rectal carcinoma, residual tumor cells were detected (R1 resection). Furthermore, the colorectal cancer of this patient showed KRAS wild-type and MMR-negative molecular classification. Therefore, postoperative treatment after surgery of the 2 primary tumors was started with a FOLFOX6/cetuximab regimen leading to disappearance of the small lung metastases and regression of liver metastases which enabled a secondary resection of the liver lesions. Due to the good systemic response with resection of the remaining lesion and the previous R1 resection of the rectal carcinoma, an additive radiochemotherapy with 5-FU and radiation up to 50.4 Gy was performed. After tumor recurrence in the liver and lung 18 months after hepatic surgery, the patient received a FOLFIRI/cetuximab regimen. In contrast to the initial therapy, a progressive myelosuppression (i.e., neutropenia, thrombocytopenia)

occurred. Although the treatment regimen led to a remarkable response, it had to be discontinued due to symptomatic septic spondylodiscitis with indication for surgery.

Hence, as a consequence, only cytostatic monotherapy (i.e., capecitabine in combination with bevacizumab) in significantly reduced dose settings was selected from now on. By means of multimodal therapies including systemic chemotherapies, radiofrequency ablation and two hepatic resurgeries, the mCRC patient obtained a longer period without treatment. In June 2015, about 15 months after the last therapeutic intervention, a multifocal recurrence of liver and lung metastases left-sided and positive intra-abdominal lymph nodes in terms of peritoneal carcinomatosis were diagnosed. Again in August 2015, a treatment schedule was started with irinotecan (in 3-week intervals with 43% dose reduction 200 mg/m<sup>2</sup>) in combination with cetuximab. Due to the occurrence of severe adverse events (leukopenia and neutropenia ≥grade 3) upon irinotecan, the patient was only treated with cetuximab in the following cycles. Since December 2015 after the diagnosis of pulmonary embolism, the patient was treated with anticoagulants, first low-molecular-weight heparins and later rivaroxaban.

In March 2016, the patient showed progressive disease in terms of liver metastases of the right hepatic lobe and he was treated by means of selective internal radiotherapy. While the liver metastases showed stable disease after selective internal radiotherapy, cancer progression occurred in lymph nodes at the hilum of the liver and in the lung. Therefore, the patient needed a novel treatment option since local interventions and standard therapies like anti-EGFR or anti-VEGF did not show disease stabilization or were intolerable during each therapeutic course (for instance, cytokine-release upon oxaliplatin re-administration).

Therefore, the first cycle of an FTD/TPI regimen for this mCRC patient (ECOG performance status 1) was started in June 2016, as the medication was available along a compassionate use program in Germany. Of note, the German market access of FTD/TPI was on August 15, 2016. Based on the summary of product characteristics and prescribing information, 70 mg/m<sup>2</sup> is recommended as the initial daily starting dose (35 mg/m<sup>2</sup>/twice daily oral) for FTD/TPI.

In view of these given data and of the long-term history of severe hematotoxicity of this cancer patient during nearly all mCRC treatment regimens, an initial absolute daily dose of 80 mg FTD/TPI was selected, though the initial daily FTD/TPI dose was 110 mg proposed for the patient due to the body surface area calculation (Table 1).

Despite the initial dose reduction, the patient experienced an asymptomatic hematotoxicity grade ≥3 which needed a 20-day dose delay before acceptable blood values were reached again for starting the next chemotherapeutic cycle with a dose reduction to 70 mg absolute daily dose of FTD/TPI. As the patient experienced the next asymptomatic neutropenia episode in cycle 3, it was decided to start with the application of 30 µg G-CSF for 3 days at day 13 within cycle 4. During the next cycle, the patient responded to the treatment with neutropenia grade 4. In view of this therapy-related severe adverse event, the G-CSF administration was extended to 5 days for this and the following cycles. Therefore, the mCRC patient experienced tolerable asymptomatic hematotoxicity episodes between cycles 6 and 10 (Table 1).

Throughout the FTD/TPI treatment of this mCRC patient, disease stabilization was monitored during cycles 3 and 6 by means of upper abdominal sonography and confirmed by CT scan (Table 1). For these required tumor re-staging purposes, marker lesions were selected.

In addition, the application of carcinoembryonic antigen (CEA) as tumor marker also underlined the stable disease findings as CEA values were measured at nearly similar levels from baseline up to the onset of cycle 5 (40–44 µg/L). Within cycle 10, when disease progression was diagnosed, the CEA value also increased up to 97 µg/L (Table 1). Of note, from baseline up to cycle 10, the mCRC patient remained in ECOG performance status 1.

## Discussion

The hematological adverse events like neutropenia were generally controlled with reductions in the dose, delays in cycle commencement or by the application of G-CSF. It is important to underline that all these different treatment characteristics in coping with severe hematological events hold true for a single mCRC patient with a prominent medical history of drug intolerances. Moreover, this patient showed disease stabilization over 10 months under FTD/TPI treatment, even in the light of an initial dose reduction to 80 mg (72% of the recommended initial dose) and further dose adaptation in cycle 2 to 70 mg and in cycle 6 to a daily dose of 60 mg FTD/TPI (55% of the recommended dose). In addition, dose reductions are generally allowed until the minimal daily dose of 40 mg/m<sup>2</sup> FTD/TPI is reached.

During the RECURSE trial, neutropenia was generally controlled with dose reductions or treatment delays; G-CSF was required in 9.4% of FTD/TPI recipients [8]. Neutropenia caused by cytotoxic drugs is of potential predictive value in several cancer types [9]. Therefore, it is additionally worth stressing the point that initial neutropenia onset as a consequence of FTD/TPI treatment is associated with survival benefit during the RECURSE trial [10]. However, this observation should not support the notion that neutropenia grade ≥3 could be aimed or tolerated for improving survival gain during FTD/TPI therapy.

In summary, FTD/TPI treatment stabilized the pre-existing cancer disease of this mCRC patient with a good quality of life for almost 1 year, with an ECOG performance status of 1 [11]. A central issue with regard to the dose setting was the prominent history of hematological toxicity along the mCRC treatment course; longer response duration might have been achieved by using an initially higher daily FTD/TPI dose. The decision leading to initial dose reduction was especially driven by the most important fact of the past occurrence of septic spondylodiscitis during chemotherapy.

## Statement of Ethics

The mCRC patient gave written informed consent.

## Disclosure Statement

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## Author Contributions

V.K. treated the patient and analyzed the patient data regarding the hematological disease and the following FTD/TPI treatment management. J.H. participated in drafting the complete article by translating anonymized patient data into the whole FTD/TPI treatment concept for the mCRC disease. W.S.-K. contributed to the case report and the patient treatment as a medical advisor. All authors read and approved the final manuscript.

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**Table 1.** FTD/TPI treatment course of a 62-year-old male patient with advanced mCRC

Patient <sup>a</sup> parameters	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7–9	Cycle 10	
Actual daily Lonsurf dose		80 mg	70 mg	70 mg	70 mg	70 mg	60 mg	60 mg	60 mg	
Lonsurf dose delay		20 days delay prior cycle 2 onset								
Hematological adverse events	Hemotoxicity grade 1	Asymptomatic hemotoxicity ≥grade 3		Asymptomatic hemotoxicity ≥grade 4; thrombocytopenia grade 1	Granulopenia	Neutropenia grade 4	Tolerable hemotoxicity	Asymptomatic hemotoxicity ≥grade 3		
Leukocyte count	3×10 <sup>9</sup> /L	1.9×10 <sup>9</sup> /L		1.4×10 <sup>9</sup> /L		2×10 <sup>9</sup> /L				
Neutrophil count	2×10 <sup>9</sup> /L	0.9×10 <sup>9</sup> /L		<0.5×10 <sup>9</sup> /L		0.9×10 <sup>9</sup> /L		Max. 0.9×10 <sup>9</sup> /L		
Thrombocyte count	112×10 <sup>9</sup> /L									
Tumor marker CEA value	40 µg/L	44 µg/L prior cycle 3 onset		44 µg/L prior cycle 5 onset				97 µg/L during cycle 10		
FDG-PET/CT	Multifocal progression			Disease stabilization			Ongoing stable disease		Disease progression	
G-CSF administration					30 µg/day for 3 days beginning at day 13 within the cycle	30 µg/day for 5 days beginning at day 13 within the cycle	30 µg/day for 5 days beginning at day 13 within the cycle	30 µg/day for 5 days beginning at day 13 within each cycle	30 µg/day for 5 days beginning at day 13 within the cycle	

CEA, carcinoembryonic antigen; <sup>18</sup>F-FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; G-CSF, granulocyte colony-stimulating factor. <sup>a</sup>Male patient (KRAS wild-type, MMR negative) with colon/rectum carcinomas and synchronous lung and liver metastases at baseline and FTD/TPI treatment onset.