Original Article

Effectiveness, safety, and prognostic factors of trifluridine/tipiracil for the treatment of patients with metastatic colorectal cancer in routine clinical practice

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: The combination of trifluridine and tipiracil is indicated in patients with metastatic colorectal cancer previously treated or non-candidates to chemotherapy and biological therapies. This study in routine clinical practice aimed to describe the effectiveness and safety of trifluridine and tipiracil and identify prognostic factors in patients with metastatic colorectal cancer in Spain.

Methods: This analysis was a retrospective, observational, multicenter study that included patients aged ≥18 years who had received treatment with trifluridine/tipiracil for metastatic colorectal cancer in third- or subsequent lines.

Results: Overall, 294 were evaluated. Trifluridine/tipiracilmedian (minimum, maximum) treatment duration was 3.5 (1.0–29.0) months, and 128 (43.5%) patients received subsequent treatments. One hundred (34%) patients showed disease control rate, and the median progression-free survival and overall survival from trifluridine/tipiracil treatment onset were 3.7 and 7.5 months, respectively. The most frequently reported adverse events were asthenia (all grades, 57.9%) and neutropenia (all grades, 51.3%). A 39.1% and 4.4% of the participants had a dose reduction and a treatment interruption due to toxicity. Patients with age ≥65 years, low tumor burden, ≤2 metastasis sites, treatment dose reduction, neutropenia, and ≥6 cycles, had significantly higher overall survival, progression-free survival, and response rate.

Conclusions: This real-life study indicates that trifluridine/tipiracil shows effectiveness and safety in treating patients with metastatic colorectal cancer. The results show a profile of metastatic colorectal cancer patients with previously unknown prognostic factors who have a more significant benefit from treatment with trifluridine/tipiracil in routine clinical practice.

Keywords: Metastatic colorectal cancer; trifluridine/tipiracil (FTD/TPI); real-world; prognostic factors

Submitted May 25, 2022. Accepted for publication Jan 09, 2023. Published online Feb 24, 2023.
doi: 10.21037/jgo-22-517
View this article at: https://dx.doi.org/10.21037/jgo-22-517

Introduction

Colorectal cancer (CRC) is the third most diagnosed cancer: in 2020, more than 1.9 million new cases and more than 900,000 deaths were reported in the world (1). In Spain, CRC is the second cancer in mortality in males and incidence in males and females, but the first in cancer death in females (2).

Approximately 30% of patients are diagnosed with metastatic disease, and recurrence will eventually occur in about half of those diagnosed at localized stages experience (3). Unresectable mCRC is fundamentally incurable, and the primary goal of treatment is to prolong survival while maintaining the quality of life (4). The 5-year overall survival (OS) rates were established at 10–15% despite advances in systemic therapy (5). Treatment of mCRC involves combined or monotherapy chemotherapy [including 5-fluorouracil (5-FU), oxaliplatin, irinotecan, and capecitabine]. First- and second-line treatments of mCRC are based on the combination of fluoropyrimidines and leucovorin with irinotecan and oxaliplatin (4,6). In addition, several biological therapies have been recently incorporated in combination with conventional cytotoxic therapy (4,7). These are monoclonal antibodies or recombinant fusion proteins targeting endothelial growth factor receptor (EGFR) or vascular endothelial growth factor/receptor (VEGF/R) (4,7). Finally, the combination of trifluridine and tipiracil (FTD/TPI) and regorafenib (a multikinase inhibitor) are approved for the treatment of patients with mCRC who have been previously treated with, or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents (8,9).

FTD/TPI demonstrated in the RECOURSE phase III study (randomized, placebo-controlled) its efficacy and safety (9). Median OS improved with FTD/TPI (7.1 *vs.* 5.3 months in the placebo arm; HR =0.68; 95% CI: 0.58–0.81; P<0.001). The median progression-free survival (PFS) was 2.0 months with FTD/TPI (*vs.* 1.7 months placebo; HR =0.48; 95% CI: 0.41–0.57; P<0.001). The most frequently treatment-associated adverse event (AE) was neutropenia (67%; 38 grade ≥3), but febrile neutropenia observed in 4% of the patients (9). A subsequent RECOURSE subanalysis showed that good prognosis factors were low tumor burden and indolent disease in the moment of FTD/TPI treatment onset (10). Another RECOURSE post-hoc analysis showed that patients with grade ≥3 neutropenia had higher median OS than patients with grade 1 neutropenia (16.4 *vs.* 9.7 months) (11).

Several recent analyses have presented the real-world treatment patterns of FTD/TPI in patients with mCRC. The analysis of a cohort of 717 patients showed that FTD/TPI is a well-tolerated therapy, but prior oxaliplatin-based chemotherapy appeared to be associated with higher discontinuation rates (12). More recently, several clinical routine analyses showed that the effectiveness and safety were comparable to the RECOURSE results (13,14). Real-world studies also suggested additional prognostic factors, as better ECOG performance status (ECOG PS), time since diagnosis of metastatic disease ≥18 months, and previous chemotherapy ≥2 months beyond progression, identified as significant variables for prediction of better OS (15). Worse prognostic factors identified by routine clinical performance analysis were ECOG PS 2, multiple metastatic sites, platelet >350,000/µL, alkaline phosphatase >500 IU/L, and carcinoembryonic antigen (CEA) >10 ng/mL (16). Lately, TAS-RECOSMO (TAS-102-FTD/TPI in REfractory COlorectal cancer Spanish MOdel) was elaborated consisting of six variables with known prognostic effect: ECOG-PS, KRAS/NRAS/BRAF mutation status, time since diagnosis of metastasis to FTD/TPI treatment onset, neutrophil-lymphocyte ratio (NLR), CEA, and alkaline phosphatase (17).

The present analysis aims to evaluate the effectiveness and safety of FTD/TPI and identify prognostic factors in routine clinical practice. This study will provide valuable information in real-world setting conditions. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-517/rc).

Highlight box

Key findings

- This real-life study analyzed 294 patients treated with trifluridine/tipiracil (FTD/TPI) for metastatic colorectal cancer (mCRC) in third- or subsequent lines. Results showed the effectiveness and satisfactory safety data after treatment. Significantly higher OS and PFS were observed in patients with age ≥65 years; treated with FTD/TPI number of cycles ≥6; reported neutropenia as an adverse; low tumor burden; ≤2 metastasis sites; and treatment dose reduction.

What is known and what is new?

- FTD/TPI is approved for treating patients with mCRC previously treated with or are not considered candidates for available therapies.
- The present study analyzed the effectiveness, new and previously identified prognostic factors, and safety of FTD/TPI in routine clinical practice.

What is the implication, and what should change now?

- Previously unknown prognostic factors identified here will be decisive in choosing the best treatment according to the specific patient's profile.

Methods

Study design

This analysis is an observational, retrospective, multicenter study of patients with mCRC treated with FTD/TPI within routine clinical practice in Andalucía (Spain), from November 2015 to May 2021, and selected consecutively from among those who met the eligibility criteria.

Participants

Patients included in the analysis met the following inclusion criteria: (I) ≥18 years; (II) diagnosis of mCRC confirmed by biopsy; (III) have been previously treated with available therapies (including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; anti-VEGF and anti-EGFR therapies); (IV) treated ≥ third line with FTD/TPI. The patients should not be treated with another investigational drug combined with FTD/TPI. FTD/TPI prescription and eventual dose reductions were carried out according to the product's SmPC and at clinical discretion.

Data source

As a retrospective study, the data source was clinical records collected from the authors' affiliations sites during routine clinical practice. These data included demographic characteristics, standard laboratory, and molecular values [including microsatellite stability (MSS) and instability (MSI), *K-RAS*, *N-RAS*, and *BRAF* mutation status], clinical status, previous and subsequent medication use, and safety data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by institutional review board of University Hospital Virgen del Rocío (Registration No. 1956-N-22). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Objectives

The main objective was to assess effectiveness of FTD/TPI in usual clinical practice in patients with mCRC by PFS, OS, and response rates. Secondary objectives were to register the safety data of FTD/TPI in routine clinical practice in these patients; to evaluate treatment duration; and analyse response rates, PFS, and OS according to subpopulations.

Variables

The main variables analysed were PFS, OS, and objective responses from FTD/TPI treatment onset according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1. For this evaluation, radiological analyses were performed by routine clinical practice every 3 months. Secondly, adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0, classified according to Medical Dictionary of Regulatory Activities (Med-DRA); exposure to FTD/TPI (number or cycles and dose reductions); and reasons for the end of treatment. High tumour burden was defined as hepatic and pulmonary infiltration, or massive hepatic infiltration.

Statistical analysis

The analysis was performed using the IBM SPSS Statistics software, Version 22.0 (IBM Corp. Armonk, NY). Data analysis was descriptive. Absolute and relative percentage frequencies described qualitative variables. The median, interquartile range (IQR), and minimum and maximum, defined quantitative variables. Survival analyses were performed using the Kaplan Meier method, providing the median, mean, 95% confidence intervals, and the number of events and number of censored cases. To compare curves in two independent groups, the Log-rank test was used to study possible statistically significant differences. To study the relationship between independent groups, *t*-test or Mann-Whitney tests were used depending on the distribution of the sample. To compare proportions and/or frequency of distributions, the Chi-square or Fisher's test were used when appropriate. COX and Log-rank regressions have been performed to assess which clinical factors are associated with PFS, OS, control rates, treatment duration and discontinuation due to progression or exitus. Statistical significance was set at $P<0.05$. The 95% CI was calculated when necessary.

Results

Patient characteristics

The study included 294 patients with mCRC being treated with FTD/TPI. The patients' median age (IQR) at diagnosis was 61.7 (53.5–69.2) years (*Table 1*). Most of them presented an ECOG PS of 0–1 (89.8%), and 164

Table 1 Characteristics of patients

Parameter	Value (N=294)
Age at diagnosis, median (IQR)	61.7 (31.4–82.0)
Age at FTD/TPI treatment	
Median (IQR)	65.2 (33.2–86.5)
≥65 years, n (%)	156 (53.1)
≥75 years, n (%)	44 (15.0)
Gender, n (%)	
Male	182 (61.9)
ECOG PS, n (%)	
0	92 (31.3)
1	172 (58.5)
2	30 (10.2)
Disease stage at diagnosis, n (%)	
I	8 (2.7)
II	33 (11.3)
III	88 (29.9)
IV	164 (55.8)
Primary tumor site	
Right colon	78 (26.5)
Left colon	216 (73.5)
K-RAS mutated status, n (%)	161 (54.8)
N-RAS mutated status, n (%)	18 (6.1)
BRAF status, n (%)	
Not mutated	246 (97.6)
Mutated	6 (2.4)
Unknown	42 (14.3)
MSS/MSI, n (%)	
MSS	190 (64.6)
MSI	25 (8.5)
Unknown	79 (26.9)
High tumor burden, n (%)	159 (54.1)
Number of metastasis sites, n (%)	
≤2	204 (69.4)
≥3	69 (23.5)
Metastasis at FTD/TPI treatment, n (%)	
Hepatic	191 (65.0)
Pulmonary	170 (57.8)
Brain	10 (3.4)
Peritoneal	91 (31.0)
Primary tumor resection, n (%)	196 (66.7)
Number of previous lines of treatment, n (%)	
2	180 (61.2)
3	82 (27.9)
≥4	32 (10.9)

IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; MSI, microsatellite instability; MSS, microsatellite-stable.

(56%) participants showed a metastatic disease stage (stage IV) at diagnosis. Most of the patients had a left-sided colon cancer location as a primary tumor site (213 patients, 73.5%), with ≤2 metastasis sites in 204 (69.4%) patients, and main metastasis location in the liver (65.0%) and the lung (57.8%). Primary tumor resection was done in 75.7% of the patients. *K-RAS*, *N-RAS* and *BRAF* mutations were identified in 54.8%, 6.4%, and 2.4% of the participants, respectively. MSI was detected in 25 (8.5%) patients. Most of the patients had been treated with 2 (n=167, 56.8%) and 3 (n=82, 27.9%) previous lines.

Median time (range) from diagnosis of metastatic and FTD/TPI treatment onset was ≥18 months in 215 (73.4%) patients (*Table 2*). FTD/TPI median (IQR) treatment duration was 3.5 (1.0–29.0) months. A total of 18 (6.1%) and 9 (3.1%) patients were treated with ≥10 and ≥13 cycles, respectively. The median (IQR) time of follow-up of patients included in the analysis was 7.5 (1.1–48.8) months. The main reason for the end of FTD/TPI treatment was disease progression (263 patients, 89.5%). Fourteen (4.8%) patients were in active treatment with FTD/TPI at the data extraction. One hundred and twenty-eight (43.5%) patients received subsequent treatments.

Effectiveness results

Progression of the disease (PD) was the most frequent

Table 2 FTD/TPI treatment data

Parameter	N=294
Time from diagnosis of metastatic disease to FTD/TPI treatment	
Months, median (IQR)	24.7 (17.2–37.4)
<18 months, n (%)	78 (26.6)
≥18 months, n (%)	215 (73.4)
FTD/TPI treatment time, months, median (IQR) (min, max)	3.5 (2.7–5.4) (1.0, 29.0)
Patients in active FTD/TPI treatment at data extraction, n (%)	14 (4.8)
Number of cycles by age, median (min, max)	
<65 years	3.0 (1.0, 13.0)
≥65 years	3.0 (1.0, 24.0)
Subsequent treatment, n (%)	128 (43.5)
RECIST response, n (%)	
CR	0 (0.0)
PR	7 (2.4)
SD	93 (31.6)
PD	194 (66.0)
Response rate (CR + PR), n (%)	7 (2.4)
Disease control rate (CR + PR + SD), n (%)	100 (34.0)

IQR, interquartile range; FTD/TPI, trifluridine/tipiracil; Max, maximum; Min, minimum; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

response in 194 patients (66%) (*Table 2*). Ninety-three (31.6%) patients and 7 (2.4%) patients achieved stable disease (SD), and partial response (PR), respectively. Any patient did not register a complete response (CR). As a result, 100 (34%) patients showed disease control rate. The median PFS was 3.73 (95% CI, 3.41–4.05) months, and the median OS from FTD/TPI treatment onset was 7.5 (95% CI, 5.1–12.4) months (*Figure 1A,1B*). According to these results, OS and PFS estimations at 3, 6, and 12 months are also shown in *Figure 1A,1B*, respectively.

Safety data

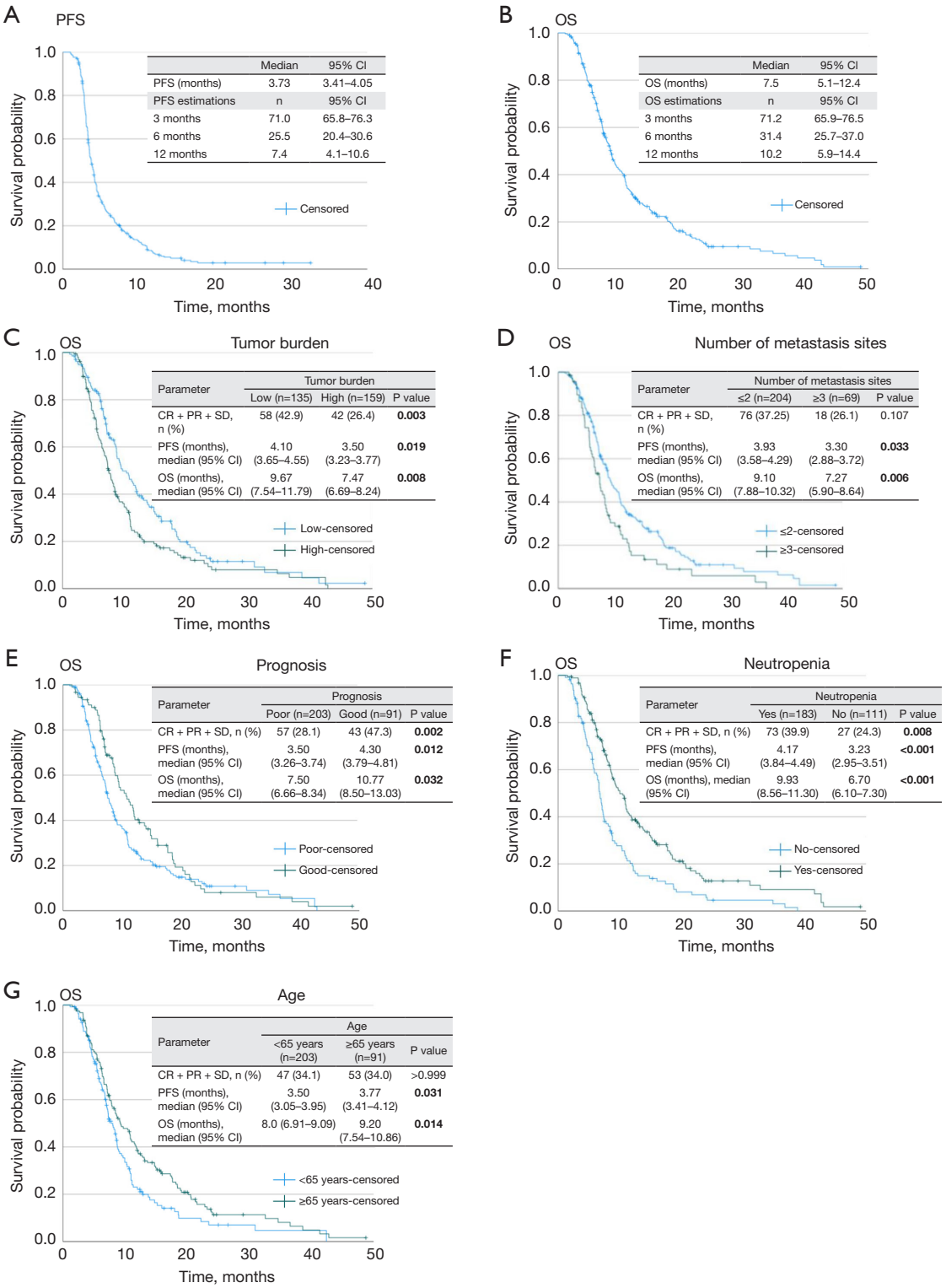
Overall, 176 (40.1%) patients reported AE of any degree. The most frequently reported AE were asthenia (57.9%), neutropenia (51.3%), diarrhea (16.5%), anemia (11.3%), and hepatic toxicity (2.6%) (*Table 3*). All of them were grade 1 to 3, with neutropenia as the most frequent grade 3 AE (32.3%). A total of 148 (50.3%) patients had a delay in the treatment administration due to toxicity, whereas 115 (39.1%) participants had a dose reduction, and 13 (4.4%) had a treatment interruption for that reason.

Analysis by subgroups

Patient profiles

Patients with age ≥65 years had a significantly higher OS (P=0.014) (*Table 4*). In the same way, patients with low tumor burden (P=0.008) also had a significantly higher OS. Remarkably, the number of metastasis sites ≤2 showed a significantly higher OS (P=0.006). In addition, patients with mutated BRAF (P=0.036) reported significant higher OS. Finally, patients that had dose reduction during the treatment with FTD/TPI (P<0.001) and reported neutropenia as an AE (P<0.001) also presented significant higher OS. No significant differences were observed in the other subgroups.

Regarding PFS, patients with age ≥65 years also presented significantly higher PFS (P=0.031). Importantly, the comparison between patients with age <75 and



	Median	95% CI
PFS (months)	3.73	3.41–4.05
PFS estimations	n	95% CI
3 months	71.0	65.8–76.3
6 months	25.5	20.4–30.6
12 months	7.4	4.1–10.6

	Median	95% CI
OS (months)	7.5	5.1–12.4
OS estimations	n	95% CI
3 months	71.2	65.9–76.5
6 months	31.4	25.7–37.0
12 months	10.2	5.9–14.4

Parameter	Tumor burden		
	Low (n=135)	High (n=159)	P value
CR + PR + SD, n (%)	58 (42.9)	42 (26.4)	**0.003**
PFS (months), median (95% CI)	4.10 (3.65–4.55)	3.50 (3.23–3.77)	**0.019**
OS (months), median (95% CI)	9.67 (7.54–11.79)	7.47 (6.69–8.24)	**0.008**

Parameter	Number of metastasis sites		
	≤2 (n=204)	≥3 (n=69)	P value
CR + PR + SD, n (%)	76 (37.25)	18 (26.1)	0.107
PFS (months), median (95% CI)	3.93 (3.58–4.29)	3.30 (2.88–3.72)	**0.033**
OS (months), median (95% CI)	9.10 (7.88–10.32)	7.27 (5.90–8.64)	**0.006**

Parameter	Prognosis		
	Poor (n=203)	Good (n=91)	P value
CR + PR + SD, n (%)	57 (28.1)	43 (47.3)	**0.002**
PFS (months), median (95% CI)	3.50 (3.26–3.74)	4.30 (3.79–4.81)	**0.012**
OS (months), median (95% CI)	7.50 (6.66–8.34)	10.77 (8.50–13.03)	**0.032**

Parameter	Neutropenia		
	Yes (n=183)	No (n=111)	P value
CR + PR + SD, n (%)	73 (39.9)	27 (24.3)	**0.008**
PFS (months), median (95% CI)	4.17 (3.84–4.49)	3.23 (2.95–3.51)	**<0.001**
OS (months), median (95% CI)	9.93 (8.56–11.30)	6.70 (6.10–7.30)	**<0.001**

Parameter	Age		
	<65 years (n=203)	≥65 years (n=91)	P value
CR + PR + SD, n (%)	47 (34.1)	53 (34.0)	>0.999
PFS (months), median (95% CI)	3.50 (3.05–3.95)	3.77 (3.41–4.12)	**0.031**
OS (months), median (95% CI)	8.0 (6.91–9.09)	9.20 (7.54–10.86)	**0.014**

Figure 1 PFS (A) and OS (B) for the patients' cohort, and OS for subgroups of patients: (C) tumor burden, (D) number metastasis sites, (E) poor and good prognosis factors, (F) neutropenia as reported AE, and (G) age <65 and ≥65 years. Bold values indicate P<0.05. CI, confidence interval; CR, complete response; FTD/TPI, trifluridine/tipiracil; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3 Main safety results

Adverse event	Overall	Grade 1–2	Grade 3–4
Hematological, n (%)			
Neutropenia	151 (51.3)	56 (19.0)	95 (32.3)
Anemia	33 (11.3)	29 (9.9)	4 (1.4)
Non-hematological, n (%)			
Asthenia	170 (57.9)	146 (49.7)	24 (8.2)
Diarrhea	49 (16.6)	46 (15.6)	3 (1.0)
ALT/AST increase	8 (2.6)	7 (2.3)	1 (0.3)
Treatment modifications due to toxicity, n (%)			
Delay			148 (50.3)
Dose reduction			115 (39.1)
Interruption			13 (4.4)
Reason end of treatment, n (%)			
Disease progression			263 (89.5)
Death			1 (0.3)
Toxicity			2 (0.7)
Clinical impairment			8 (2.7)
Complication not related to disease progression			5 (1.7)

ALT, alanine transaminase; AST, aspartate aminotransferase.

≥75 years showed no significant differences. Low tumor burden, and, and MSS were also registered with significant higher PFS (P=0.019; and P=0.005, respectively). In the same way, the number of metastasis sites ≤2 showed higher PFS (P=0.033). Finally, significant higher PFS was reported in patients with treatment dose reduction, and patients who had reported neutropenia as an AE (P<0.001).

Consequently, subpopulations' analysis showed that patients with high tumor burden showed significantly more PD and less SD and PR (P=0.003) (*Figure 1C*). As a result, PFS and OS from FTD/TPI treatment onset were significantly higher in patients with low tumor burden *vs.* patients with higher tumor burden (P=0.019; and P=0.008, respectively) (*Figure 1C*). In the same way, PFS and OS from FTD/TPI treatment onset were significantly higher in patients with ≤2 metastasis sites *vs.* ≥3 sites (P=0.033; and P=0.006, respectively) (*Figure 1D*).

Poor and good prognosis profiles (high or low tumor burden, or time from diagnosis of metastasis <18 or ≥18 months, respectively) also showed significant differences (*Figure 1E*). Patients with poor prognosis factors (n=203) showed more PD, and less SD and PR, than patients with good prognosis factors (n=91) after treatment with FTD/TPI (P=0.002). Therefore, the patients with poor prognosis factors reported a significantly lower PFS (P=0.012) and lower OS from FTD/TPI treatment onset (P=0.032) (*Figure 1E*). Taking as a reference the subanalysis previously performed with data from the RECOURSE study (10), for the present study, we analyzed the impact of the combination of the definition used here for high or low tumor and the time since diagnosis of metastasis (<18 or ≥18 months) (Table S1). A statistically significant difference was obtained for both the response results and the PFS and OS determinations (P=0.002, P=0.012, and P=0.032, respectively).

The presence of haematological toxicity, namely the presence of neutropenia (any grade), also shows a statistically significant difference in both response rate, PFS and OS, versus no presence (P=0.008; and P<0.001, respectively) (*Figure 1F*).

In the same way, patients' age suggested significant differences in FTD/TPI-related PFS and OS, specifically

Table 4 OS and PFS according to subgroups

Parameter	OS			PFS		
	Median (months)	95% CI	P value	Median (months)	95% CI	P value
Age			0.014*			0.031*
<65 years	8.00	6.91–9.09		3.50	3.05–3.95	
≥65 years	9.20	7.54–10.86		3.77	3.41–4.12	
Age			0.912			0.356
<75 years	8.50	7.68–9.32		3.73	3.39–4.075	
≥75 years	8.57	5.88–11.25		3.63	2.89–4.38	
Time from diagnosis of metastatic disease			0.231			0.169
<18 months	7.03	5.42–8.65		3.47	3.21–3.72	
≥18 months	8.80	7.38–9.86		3.87	3.52–4.22	
Disease stage			0.130			0.312
I	12.50	10.975–14.025		7.47	0.91–14.03	
II	10.67	8.56–12.775		3.73	3.37–4.10	
III	7.90	5.52–10.28		3.87	3.035–4.70	
IV	7.83	6.77–8.90		3.70	3.27–4.13	
Tumor burden			0.008*			0.019*
Low	9.67	7.54–11.79		4.10	3.65–4.55	
High	7.47	6.69–8.24		3.50	3.23–3.77	
Number of metastasis sites			0.006*			0.033*
≤2	9.10	7.88–10.32		3.93	3.58–4.29	
≥3	7.27	5.90–8.64		3.30	2.88–3.72	
Primary tumor site			0.908			0.400
Right	9.67	7.22–12.11		4.07	3.45–4.68	
Left	8.43	7.58–9.29		3.73	3.44–4.03	
K-RAS status			0.471			0.826
Not mutated	8.63	6.31–10.95		3.50	3.13–3.87	
Mutated	8.43	7.58–9.29		3.93	3.51–4.36	
N-RAS status			0.883			
Not mutated	8.43	7.62–9.25		3.73	3.42–4.04	0.924
Mutated	8.57	6.065–11.07		2.87	1.97–3.77	
BRAF status			0.036*			0.502
Not mutated	8.43	7.59–9.28		3.70	3.41–3.99	
Mutated	18.43	0.00–42.28		4.07	2.15–5.99	
MSS/MSI			0.004*			0.005*
MSS	9.93	8.49–11.38		3.73	3.375–4.09	
MSI	6.77	5.91–7.62		3.30	2.54–4.06	

Table 4 (*continued*)

Table 4 (*continued*)

Parameter	OS			PFS		
	Median (months)	95% CI	P value	Median (months)	95% CI	P value
FTD/TPI treatment line			0.746			0.827
≤ Third line	8.43	7.55–9.315		3.87	3.47–4.27	
> Fourth line	9.20	7.55–10.85		3.47	3.12–3.81	
FTD/TPI number of cycles			<0.001*			<0.001*
≤5	7.07	6.57–7.57		3.30	3.16–3.44	
≥6	17.63	13.80–21.46		9.33	4.65–11.01	
FTD/TPI dose reduction			<0.001*			<0.001*
No	7.07	6.42–7.71		3.33	3.16–3.505	
Yes	11.47	9.38–13.55		4.50	3.68–5.32	
Neutropenia as adverse event			<0.001*			<0.001*
No	6.70	6.01–7.30		3.23	2.95–3.51	
Yes	9.93	8.56–11.30		4.17	3.84–4.49	

*P<0.05. CI, confidence interval; FTD/TPI, trifluridine/tipiracil; MSI, microsatellite instability; MSS, microsatellite-stable; PFS, progression-free survival; OS, overall survival.

in the case of patients <65 and ≥65 years (P=0.031; and P=0.014, respectively) (*Figure 1G*).

Factors influencing response to FTD/TPI treatment

The univariate and multivariate analyses were performed with the different factors and patients' subpopulations analyses (*Table 5*). According to these analyses, age ≥65 years (HR =0.716, P=0.013) and any grade of neutropenia as an AE (HR =0.598, P<0.001), were significantly better prognostic factors in terms of progression of disease. Regarding PFS, registered MSI or metastasis sites ≥3 were a significantly poorer prognostic factor in terms of PFS (HR =1.691, P=0.020; and HR =1.411, P=0.042, respectively).

Regarding FTD/TPI treatment duration, MSS was a better prognostic factor (OR =0.177, P=0.004). In contrast, a median time from diagnosis of metastasis ≥18 months and absence of neutropenia as reported AE were poorer prognostic factors (OR =5.752, P<0.001; and OR=3.186, P=0.027, respectively).

Discussion

This real-world analysis studied the effectiveness and safety of FTD/TPI for treating patients with mCRC.

Main clinical results indicated a SD and PR in 31.6% and 2.4% of the participants, respectively, and a disease control rate of 34%. Results also showed a median PFS and OS of 3.73 and 7.5 months, respectively. These results are similar to those of previous pivotal and real-world studies (9,12,16,18-20). However, the design and patient's profile of these previous studies are different, as they are randomized controlled trials (RCT) (9), post-hoc analyses (10), retrospective observational studies (12), and data collection from compassionate use programmes (18-20). A systematic meta-analysis of RWD with 1,008 patients indicated that the FTD/TPI effectiveness in late-stage mCRC in daily practical settings reflected the outcomes in RECOURSE (21). The pooled median OS and PFS were 6.6 months (95% CI: 6.0–7.5) and 2.2 months (95% CI: 2.1–2.3), respectively. The results obtained in our analysis are in the same way or even better than this real-world meta-analysis, demonstrating that routine clinical practice further optimises FTD/TPI use in mCRC. In contrast, disease control was achieved in 44% of patients in RECOURSE (9). A logical contrast between real-life analyses and RCTs is the difference in time of patients' assessments. It should be noted that the radiologic assessments were established in the RECOURSE study protocol every 8 weeks, whereas in the common routine clinical practice, at least in the centres that participated in the present analysis, these reviews are established every 3 months.

Table 5 Multivariate analysis

Parameter	HR	95% CI	P value
Predictor of prognosis: OS			
Age ≥65 *vs.* <65 years	0.716	0.551–0.931	0.013
Hematological adverse event *vs.* non-hematological	0.598	0.460–0.777	<0.001
Predictor of prognosis: PFS			
MSS *vs.* MSI	1.691	1.087–2.631	0.020
Number or metastasis sites ≥3 *vs.* ≤2	1.411	1.013–1.966	0.042
Hematological adverse event *vs.* non-hematological	0.486	0.353–0.669	<0.001
Predictor of effectiveness: FTD/TPI treatment duration			
MSI *vs.* MSS	0.177	0.054–0.578	0.004
Time from diagnosis of metastatic ≥18 *vs.* <18 months	5.752	2.078–15.923	<0.001
Non-hematological adverse event *vs.* hematological	3.186	1.143–8.882	0.027

CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; MSS, microsatellite stability; MSI, microsatellite instability; PFS, progression-free survival; PR, partial response; OR, odds ratio; OS, overall survival; SD, stable disease.

However, as discussed above, in several retrospective analyses in routine clinical practice in patients with the same profile, the disease control was achieved in proportions ranging from 37.6% to 70.8% (15,16,22).

It is also important to note that 43.5% of the patients included in the present analysis had subsequent treatments, which might partially contribute to the observed effectiveness data. Remarkably, a significant proportion of these treatments were mainly retreatments with agents used in previous lines and, to a lesser extent, participation in clinical trials with new therapies in clinical development.

Analysis by subgroups suggested that patients with age ≥65 years, low tumor burden, ≤2 metastasis sites, treated with FTD/TPI number of cycles ≥6, treatment dose reduction, and reported neutropenia as an AE, had significantly higher OS and PFS. The results also indicated that patients with age ≥65 years, treated with an FTD/TPI number of cycles ≥6 cycles, and reporting neutropenia as an AE, had a lower risk of PD or death. Finally, patients with a median time from diagnosis of metastasis ≥18 months, and AE without neutropenia had a higher risk of shorter FTD/TPI treatment duration.

The difference observed in patients ≥65 years compared to patients <65 years could be partially explained by the fact that among the group of younger age the percentage of patients with stage IV at diagnosis was significantly higher (62.8% *vs.* 49.3% in the group of ≥65 years). In addition, among the participants <65 years the percentage of patients that received a subsequent treatment was lower (39% *vs.* 47%).

The definition of high tumor burden was established particularly for the present data analysis as hepatic and pulmonary infiltration, or massive hepatic infiltration. This definition was established according to experience in routine clinical practice in mCRC management consultation and to explore a prognostic factor with clinical utility different from those previously published (10,16). Since significant differences in PFS, OS, and response rate are observed in favour of patients with low tumor burden, this definition may be necessary when making practical decisions in this patient profile.

The description of the real-life characteristics of this cohort of patients also showed that although the median time of treatment with FTD/TPI were 3.5 months, some patients were treated for 29 months. It is also remarkable that patients who had to reduce treatment dose despite having to adjust the dosage, the effectiveness is maintained. Consequently, a good choice of treatment according to each patient's specific characteristics may be crucial.

Previous post-hoc exploratory analysis of prognostic factors on the RECOURSE trial showed that low tumor burden and indolent disease were good prognosis factors, whereas ≥3 metastatic sites and <18 months from first metastasis were poor prognosis factors (10). Patients with good prognosis factors improved PFS and OS with FTD/TPI treatment compared to placebo. Together, these and our analysis suggests that RWD is more realistic as the

population has less controlled characteristics than the RECOURSE study and the post-hoc analyses.

Importantly, safety results were consistent with previous pivotal and real-world analyses. The most frequent AEs were grade 1 to 3 asthenia, neutropenia, and diarrhea. The treatment was manageable since only 4.4% of participants had a treatment interruption for toxicity. Moreover, results indicated a significant association of neutropenia as a reported AE, higher OS and PFS, and a lower risk of progressive disease or death. Overall, this is in line with previous findings, which indicated that neutropenia caused by FTD/TPI during the first cycle was associated with better efficacy. Consequently, neutropenia may be a surrogate marker for adequate antitumor doses of FTD/TPI (23).

Some limitations of the present analysis are inherent to the retrospective design, and found in studies with a similar design. The information collected and used in the different analyses presented here was limited by the presence in the medical records of the participating patients. In particular, in the case of safety data, although information was available for all patients, it could not be collected in the same way as would be done in a prospective study or a controlled clinical trial. Moreover, the authors consider that some of the sub-analyses cannot be considered since they were performed with data of a few patients (i.e., MSS/MSI and BRAF status, in accordance with the RECOURSE study and other real-life analyses). In addition, concerning patients with mutated BRAF and/or MSI, it is a limitation that the participants were not treated with targeted therapies or immunotherapy, respectively, due to the lack of availability of these treatments. The absence of an active comparator or placebo arm makes drawing formal conclusions difficult. In addition, an external validation study for the response outcomes and prognostic factors described here would be desirable.

In contrast, one of the main strengths of the present analysis is that this is a real-life setting study describing the usual clinical practice with FTD/TPI. The total number of patients included in the cohort (n=294) represents a significant strength compared to other recently published RWD for FTD/TPI. In addition, patients included in the study comprised a broader and more heterogeneous population than in the pivotal studies.

Conclusions

This study in real-life conditions suggests that FTD/TPI is effective in treating patients with mCRC. In the present analysis, we have not only analyzed prognostic factors previously identified and published in RWD cohorts but also searched for new factors and combinations of these that could have an impact on the clinical management of FTD/TPI treatment. Consequently, the results indicate several previously unknown prognostic factors and others that corroborate those identified in previous real-world studies. All this information will be decisive in choosing the best treatment according to the specific profile of each patient. FTD/TPI had a safety profile that was commensurate with previous studies.

Acknowledgments

The authors want to thank GEODA (Grupo Español de Oncología Digestiva de Andalucía) for making this work possible. The authors want to thank Alicia Subtil-Rodríguez of Evidenze Research for editorial assistance with this manuscript.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-517/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-517/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-517/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-517/coif). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by institutional review board of University Hospital Virgen del Rocío (Registration No. 2071-N-22). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Open Access Statement: This is an Open Access article

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Cite this article as: Martínez-Pérez J, Espinosa-Montaño M, Luque-Caro N, Aviñó-Tarazona V. Effectiveness, safety, and prognostic factors of trifluridine/tipiracil for the treatment of patients with metastatic colorectal cancer in routine clinical practice. J Gastrointest Oncol 2023;14(2):692-704. doi: 10.21037/jgo-22-517

Supplementary

Table S1 Patient's subpopulation analysis (prognosis factors)

Parameters	Poor (n=203) (high tumor burden* or time from diagnosis of metastatic <18 months)	Good (n=91) (low tumor burden* or time from diagnosis of metastatic ≥18 months)	P value
PD, n (%)	146 (71.9)	48 (52.7)	
SD, n (%)	55 (27.1)	38 (41.8)	0.002
PR, n (%)	2 (1.0)	5 (5.5)	
PFS (months), median (95% CI)	3.50 (3.26–3.74)	4.30 (3.79–4.81)	0.012
OS from FTD/TPI treatment onset (months), median (95% CI)	7.50 (6.66–8.34)	10.77 (8.50–13.03)	0.032

*, high/low tumour burden was defined as presence or not of hepatic and pulmonary infiltration, or massive hepatic infiltration. CI, confidence interval; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease; FTD/TPI, trifluridine/tipiracil.

https://dx.doi.org/10.21037/jgo-22-517