Recenti Prog Med 2022; 113: 380-382

Long-term survivors of metastatic colorectal cancer treated with trifluridine/tipiracil

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Received on March 6, 2022. Accepted on March 18, 2022.

Dear Editor

recently, the introduction of trifluridine/tipiracil (TFD/TPI) in heavily pretreated metastatic colorectal cancer (mCRC) have improved rates of survival and it has become one of the treatment options in this setting[1]. Median overall survival (OS) in the pivotal phase III randomized controlled trial (RCT) was 7.1 months for TFD/TPI versus (vs.) 5.3 months of placebo (HR=0.68, 95% CI: 0.58-0.81, p<0.001). A further data of interest is represented by the percentage of median OS at 12 months: 26.6% for TFD/TPI vs. 17.6% of placebo. This introduces the concept of long-term survivors of mCRC treated with TFD/TPI. Currently there are no data in clinical practice relating to this type of patient. The only predictive data of response is represented by the onset of neutropenia with the first courses of chemotherapy[2,3].

The aim of this paper was to evaluate the subgroup of long-term survivors of mCRC treated with TFD/TPI in our daily clinical practice, in order to be able to identify potential predictive factors. To our knowledge, no studies that have investigated long-term survivors of mCRC treated with TFD/TPI in real life are reported in literature.

A retrospective analysis of all consecutives patients with mCRC and treated with TFD/TPI followed at the Medical Oncology Unit of Mater Salutis Hospital, Legnago (Italy) between July 2017 and September 2021 was performed. All informations were obtained from case history and reviewed the patient's medical history. Follow-up time (FUT) was define as the time patients have been followed at Our Institution. Overall Survival (OS) was estimated starting from the first day of the first cycle of TFD/TPI to the last visit or patient's death date, censoring surviving patients at the time of last follow-up. We divided the patients into 2 groups: patients with progression free survival (PFS) less than 6 months (group 1) and patients with PFS>=6 months (group 2). We chose the value of 6 months as discriminatory for PFS, as it is already arbitrarily recognized in the literature for patients with metastatic cancer[4]. A univariate analysis for OS, considering all the different prognostic factors, was estimated according to the Kaplan-Meier method with statistical significance (p<0.05) of differences evaluated by log-rank test, censoring surviving patients at the last follow-up time. Chi-square test or Fisher's exact tests, with significance set at α=5%, were used to estimate a possible any possible relationship between results and the different prognostic variables.

We evaluated 33 patients, 21 patients (63.6%) belonging to group 1 and 12 (36.4%) to group 2.

Group 1. Median FUT was 25.16 months (range: 4.08-89.47 months). At the last FUT 16 patients (76.2%) were deceased and 5 patients (23.8%) were alive. Median OS was 5.10 months (range: 1.38-17.60 months). Median age was 64 years (range: 31-82). Seven patients (33.3%) were female. Right colon (38.1%) was the main site of the disease. Liver (57.1%) was the main site of metastases. The patients were mostly KRAS mutated (66.7%), NRAS wild-type (61.9%) and BRAF wild-type (100.0%). Eastern Cooperative Oncology Group Performance Status (ECOG PS) was mostly 0-1 (90.5%) before starting treatment with TFD/TPI and remained 0-1 (61.9%) also after the end of treatment with TFD/TPI. Serious adverse events (SAEs) occurred in 19.1% of patients, with only 4.8% of dose reduction. The case study is reported in table 1.

Group 2. Median FUT was 72.53 months (range: 12.17-113.42 months). At the last FUT 8 patients (66.7%) were deceased and 4 patients (33.3%) were alive. Median OS was 25.23 months (range: 6.88-38.36 months). Median age was 62 years (range: 29-81). Six patients (50.0%) were female. Left colon (50.0%) was the main site of the disease. Liver (41.6%) was the main site of metastases. The patients were KRAS wild-type in the 50.0%, mostly NRAS wild-type (75.0%) and BRAF wild-type (91.7%). All patients (100.0%) had a ECOG PS=0-1 before starting treatment with TFD/TPI and remained 0-1 (91.7%) also after the end of treatment with TFD/TPI. SAEs occurred in 75% of patients (exclusively grade 3 and grade 4 neutropenia), with dose reduction in 100.0%. In the group 2, 7 patients (58.3%) had PFS>= 12 months (range: 12.20-32.14 months), with ECOG PS=0-1 both before and after the treatment with TFD/TPI ain all patients (100.0%) and all (100.0%) with grade 3 and grade 4 neutropenia as SAE. The case study is reported in table 1.

At the chi-square test there was statistical relationship between both ECOG PS before (p=0.021) and

Table 1. The general case study.

Variable	Value	PFS< 6 months	PFS>= 6 months
		N° (%)	N° (%)
Sex	Female	7 (33.3)	6 (50.0)
	Male	14 (66.7)	6 (50.0)
Site	Right colon	8 (38.1)	3 (25.0)
	Left colon	6 (28.6)	6 (50.0)
	Rectum	7 (33.3)	3 (25.0)
Surgery for primary site	Yes	16 (76.2)	11 (91.7)
	No	5 (23.8)	1 (8.3)
Prevalent site of metastses	Liver	12 (57.1)	5 (41.6)
	Lymph-node	4 (19.0)	2 (16.7)
	Peritoneum	3 (14.3)	3 (25.0)
	Lung	2 (9.5)	2 (16.7)
KRAS	Wild-type	7 (33.3)	6 (50.0)
	Mutated	14 (66.7)	6 (50.0)
NRAS	Wild-type	13 (61.9)	9 (75.0)
	Mutated	0 (0.0)	1 (8.3)
	Missing	8 (38.1)	2 (16.7)
BRAF	Wild-type	21 (100.0)	11 (91.7)
	Mutated	0 (0.0)	1 (8.3)
ECOG PS before TFD/TPI	0-1	19 (90.5)	12 (100.0)
	≥2	2 (9.5)	0 (0.0)
ECOG PS after TFD/TPI	0-1	13 (61.9)	11 (91.7)
	≥2	8 (38.1)	1 (8.3)
Type of response	CR	0 (0.0)	1 (8.3)
	PR	2 (9.5)	3 (25.0)
	SD	1 (4.8)	8 (66.7)
	PD	18 (85.7)	0 (0.0)
SAEs	Neutropenia g.3	2 (50.0)	4 (44.4)
	Neutropenia g.4	0 (0.0)	5 (55.6)
	Diarrhea g.3	2 (50.0)	0 (0.0)
Dose reduction	Yes	1 (4.8)	5 (41.7)
	No	20 (95.2)	7 (58.3)

Legend: N°= number of patients; PFS= progression free survival; ECOG PS= Eastern Cooperative Oncology Group; TFD/TPI= trifluriidina/tipiracil; CR= complete response; PR= partial response; SD= stable disease; PD= progression of the disease; SAEs= serious adverse events.

after (p=0.005) the treatment with TFD/TPI and the outcome (PFS and OS), such as between the objective response rate (ORR) and the outcome (p<0.001). This statistical relationship was also confirmed for grade 3 and grade 4 neutropenia (p<0.001). At the univariate analysis, the PFS was confirmed as a surrogate endpoint of OS in mCRC patients treated with TFD/TPI (p<0.001) (figure 1).

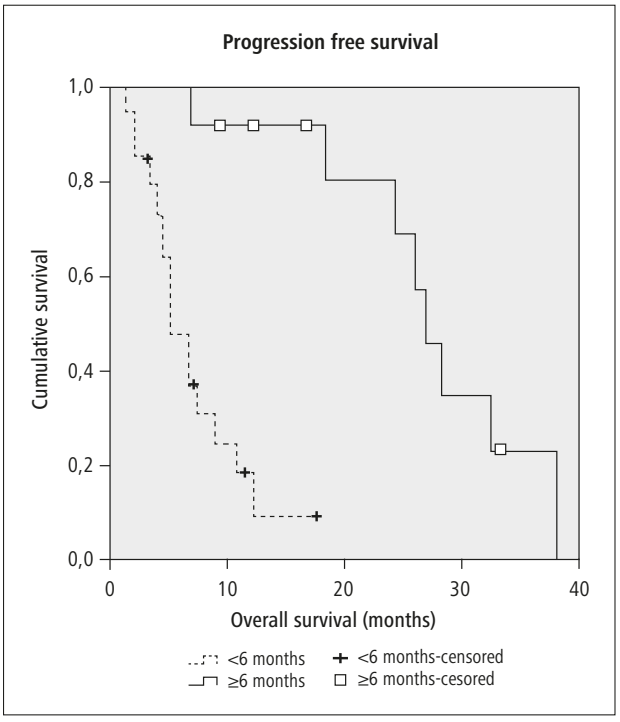

Figure 1. Univariate analysis for OS in the 2 groups.

Our study sought to identify predictive factors of response to TFD/TPI in mCRC patients, based on the finding in clinical practice of a percentage (higher in our experience than that reported in the pivotal phase III randomized controlled trial[1]) of long-term survivors patients treated with TFD/TPI. What emerges is the role of the onset of grade 3 and grade 4 neutropenia (already known[2,3]). What emerges as novelty is the ECOG PS before and after the treatment with TFD/TPI. In particular, it is possible that a good ECOG PS after the end of the treatment with TFD/TPI leave the patient in good condition to be able to carry out subsequent lines of treatment and this inevitably increases OS. Also patients who responded (CR and PR) to TFD/TPI have had an increase in OS.

We are aware of the limitations of a retrospective study, the small size of the cohorts and the fact that data coming from a single Institution could reflect only the habits of that particular set of physicians; on the contrary, studies like the above, though the analysis of not selected case study, are able to evaluate the oncological approach in a real world clinical practice. In facts, the patients described here represent the complete series and consecutive of patients who underwent a systemic treatment at our Unit in the considered time frame, were treated in a homogeneous way and carefully staged before the beginning of treatment and at regular intervals thereafter. Furthermore, follow-up was complete in all patients.

In conclusion, the search for a predictor of response to TFD/TPI that is able to justify long surviving mCRC patients remains difficult to find. The onset of severe neutropenia (grade 3 and 4) confirmed to predicted survival. ECOG PS before and after the treatment with TFD/TPI may also be able to be a predictive factor, such as ORR. These factors could in fact help us to identify those mCRC patients who could benefit most from treatment with TFD/TPI.

Authorship: all authors contributed equally to (1) conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the version to be published.

Conflict of interests: the authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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