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EFFICACY AND TOLERABILITY OF TRIFLURIDINE/TIPIRACIL IN PATIENTS WITH REFRACTORY METASTATIC COLORECTAL CANCER AT THE GENERAL HOSPITAL OF ŠIBENIK-KNIN COUNTRY

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Summary

In randomized clinical trials, trifluridine / tipiracil (TT) demonstrated beneficial effects on progression-free survival (PFS) and overall survival (OS) in patients with refractory metastatic colorectal cancer (mCRC). The aim of this unicentric study was to evaluate the efficacy and safety of TT in patients with refractory mCRC in everyday clinical practice. Treatment outcomes of 20 patients were retrospectively analyzed. The median OS was 6.25 months (range 1-18) and the median PFS was 3 months (range 2–13). The most common (80%) side effect of TT was neutropenia and 35% of patients had neutropenia grades 3 of 4; however, only two patients (10%) had neutropenic fever and no deaths were attributable to neutropenia. In conclusion, treatment outcomes in this real-life study seem comparable to those from randomized clinical trials.

KEYWORDS: *refractory metastatic colorectal cancer; colorectal cancer treatment; trifluridine/tipiracil*

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death in the world(1,2). In Croatia it is third most common cancer in men and second in women(2). Despite treatment and diagnostic advances, the mortality rates of mCRC remain high, with a patient survival of 24–30 months(3-6). The treatment backbone for patients with mCRC is irinotecan- and oxaliplatin-based therapy in combination with fluoropyrimidines and molecular targeted therapy(5-8). Treatment options for mCRC after progression to standard therapy is limited. Also, it is important to emphasize that quality of life is an important outcome during the later-lines of therapy. Trifluridine/tipiracil (TT) is an orally administered cytotoxic agent approved for treatment of patients with refractory mCRC.

The aim of this unicentric study was to evaluate efficacy and safety of TT in patients with refractory mCRC in everyday clinical pratice.

PATIENTS AND METHODS

Treatment outcomes of patients with refractory mCRC at the General Hospital of Šibenik-Knin County from March 2018 to March 2021 were retrospectively analyzed. PFS was defined as the time from first TT application until disease progression, while OS was measured as the time from first TT application until death or the last follow-up visit. The results were presented by descriptive statistical methods and the survivals between the groups were compared with the Kaplan-Meier method and the log-rank test. Statistical calculations were performed with MedCale Software, version 20.008 (Ostend, Belgium) and p-values <0.050 were considered statistically significant for all presented.

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Table 1.

Patient characteristics

		N (%)
Age	Median	67
	Range	53-83
Gender	Male	14 (70)
	Female	6 (30)
ECOG status	0	4 (20)
	1	13 (65)
	2	3 (15)
Primary tumor location	Rectum	6 (30)
	Left colon	10 (50)
	Right colon	4 (20)
RAS status	*Wild* type	3 (15)
	Mutation	17 (85)
Time from diagnosis of metastasis to initiation of treatment	> 18 month	12 (60)
	≤ 18 month	8 (40)
Number of previous lines of therapy	1	1
	2	16
	≥3	3

RESULTS

A total of 20 patients with mCRC were treated with TT; the median age was 67 years (range 53–83), and the majority were male (70%). The patients were in good general condition (performance status 0-2). Ten patients (50%) had left-sided cancer, six patients had rectal cancer (30%) and four patiens had primary cancer located in the right colon (20%). The most common site of metastasis was the liver (75%) and in three patients it was the only site. Most patients presented with multiple metastases (95%). Mutation in the RAS gene was detected in 85% of patients; three patients were RAS *wild* type. The majority of patients (80%) received TT in the third line of treatment, one patient received it in the second line and for three patients (15%) it was the fourth line or more. The first line irinotecan-based chemotherapy was administered to the majority of patients (80%) and four patients received oxaliplatin-based therapy. Thirteen patients (65%) received biological therapy. In 60% of patients time from diagnosis of metastasis to initiation of TT treatment was ≥ 18 month and in 40% was < 18 month. The median number of TT cycles received was 3 (range 1–13),

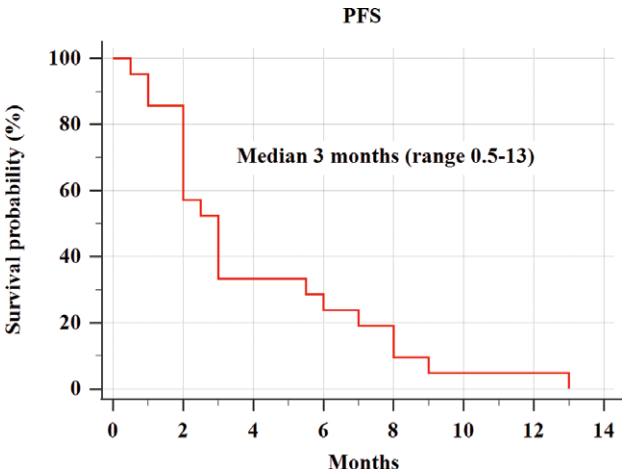

Figure 1. Progression-free survival (PFS) of the study population. The Kaplan-Meier and the log rank tests were used.

and more than one-third of patients (35%) achieved a therapeutic response; two partial response, and five patients stable disease. Patients characteristics are summarized in Table 1.

All patients progressed and five of them (25%) died during the follow-up. The median PFS and OS were 3 months (range 2–13) and 6.25 months (range 1-18), respectively, as shown in Figure 1. Male sex (HR 4.45; p = 0.026), better performance status (p = 0.021), neutropenia grade ≥2 (HR 5.64; p = 0.013) and positive therapeutic response to TT (HR 12.76; p <0.001) were associated with better PFS. There were no significant correlations of PFS with age, previous treatment duration and RAS status (p>0.050 for all analyses). The most common (80%) side effect of TT was neutropenia; grade 3 in 30% and grade 4 in 5% of patients, while neutropenic fever was recorded in only two patients (10%). There were no deaths associated with neutropenia.

DISCUSSION

The improved treatment outcomes in randomized trials are sometimes hard to achieve in everyday clinical practice; thus, observational studies and retrospective analyses are often needed to assess the effects of anti-cancer drugs in the real-life setting. In clinical trials TT demonstrated a beneficial effect on PFS and OS in patients with mCRC refractory to standard chemotherapy(9-15). In randomized phase III clinical trial (RESOURCE)

TT demonstrated a beneficial effect on progression-free survival (PFS, 2.0 month) and overall survival (OS, 7.1 month) in patients with mCRC refractory to standard chemotherapy. The overall survival benefit with TT was observed in all prespecified subgroups, including subgroups defined according to each of the three stratification factors (i.e., KRAS status, time between first diagnosis of metastases and randomization, and geographic region). In the multivariate Cox regression analysis, none of the factors were identified as being predictive. Three factors were identified as prognostic: time since diagnosis of first metastasis, ECOG performance status, and number of metastatic sites. The most frequently observed clinically significant adverse events (grade 3 or 4) associated with TT were neutropenia, which occurred in 38% of those treated, 4% of the patients had febrile neutropenia, and one death related to TT was reported(9,10). The TERRA study confirmed that TT has a statistically significant survival benefit compared with placebo in Asian patients with mCRC refractory or intolerant to standard chemotherapies, regardless of exposure to biologic therapy. The safety profile is similar to previous reports(16-18). The primary endpoint in PRECONNECT study was safety. It is ongoing study with 793 patients included. The median duration of treatment was 2.8 months. Drug-related adverse events grade 3 and 4 occurred in 73,9% of patients. Neutropenia was the most common side effect, with grades 3 and 4 being recorded in 39.1 % of patients. Median time to Eastern Cooperative Oncology Group performance status deterioration (≥2) was 8.9 months. There was no clinically relevant change from baseline in quality of life(19-21).

Similarly, these results gathered from a real-life setting seem comparable to those from clinical trials and indicate that refractory mCRC patients treated with TT in the community setting can have improved clinical outcomes as well. In our study there were no significant correlations of PFS with age, previous treatment duration and RAS status. A possible reason is the small number of patients. On the other hand male sex, better performance status, neutropenia grade ≥2 and positive therapeutic response to TT were associated with better PFS. Lightly lower incidence of neutropenia in our study could be explained with the small number of heavily pretreated patients included in the study.

In conclusion, this study confirmed favourable clinical outcomes of patients with refractory mCRC treated with TT in the real-life setting with manageable toxicities.

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Sažetak

RETROSPEKTIVNA ANALIZA UČINKOVITOSTI I PODNOŠLJIVOSTI TRIFLURIDIN/TIPIRACILA U BOLESNIKA S REFRAKTORNIM METASTATSKIM KOLOREKTALNIM KARCINOMOM U OPĆOJ BOLNICI ŠIBENSKO-KNINSKE ŽUPANIJE

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U randomiziranim kliničkim studijama trifluridin/tipiracil (TT) je pokazao povoljan učinak na preživljenje bez progresije bolesti (PFS) i na ukupno preživljenje (OS) u bolesnika s refraktornim metastatskim kolorektalnim karcinomom (mKRK). Cilj ovog unicentričnog istraživanja bio je procijeniti učinkovitost i sigurnost primjene TT kod bolesnika s refraktornim mKRK u svakodnevnoj kliničkoj praksi. Retrospektivno su analizirani ishodi liječenja 20 bolesnika. Medijan OS bio je 6.25 mjeseci (raspon 1-18) a medijan PFS 3 mjeseca (raspon 2-13). Najčešća (80%) nuspojava TT bila je neutropenija, u 35% bolesnika gradusa 3 i 4. Ipak, u samo dva bolesnika (10%) zabilježena je neutropenična vrućica, a nijedan bolesnik nije preminuo zbog neutropenije. Zaključno, ishodi liječenja bolesnika s mKRK s TT u svakodnevnom kliničkom radu usporedivi su s onima iz randomiziranih kliničkih studija.

KLJUČNE RIJEČI: *refraktorni metastatski kolorektalni karcinom; liječenje kolorektalnog karcinoma; trifluridine/tipiracil*