Trifluridine/tipiracil in metastatic colorectal cancer: an updated multicentre real-world analysis on efficacy, safety and predictive factors

Chara Stavraka[1], Athanasios Pouptsis[1], Alicja Synowiec[2] , Vasileios Angelis[2], Liyana Satterthwaite[3], Sam Khan[4], Meera Chauhan[4], Chloe Holden[5], Sally Young[5], Christina Karampera[1], Maria Martinou[6], Tina Mills-Baldock[6], Mark Baxter[7], Bryony Eccles[5], Tim Iveson[3], Kai-Keen Shiu[8], Mark Hill[2], Sherif Abdel-Raouf[6], Anne Thomas[9] ,Paul J. Ross[1]

1.Guy's and St Thomas' NHS foundation Trust, London; 2. Maidstone and Tunbridge Wells NHS Trust, Maidstone; 3.Southampton University Hospitals NHS Trust, Southampton; 4. Leicester Royal Infirmary, Leicester; 5. Poole Hospital NHS Foundation Trust, Poole; 6. Queen's Hospital, Essex; 7.Beatson West of Scotland Cancer Centre, Glasgow; 8.University College London Cancer Institute, London; 9.Leicester Cancer Centre, University of Leicester

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ABSTRACT

Background: The orally administered combination Trifluridine and Tipiracil hydrochloride (TAS-102) has been approved as third line treatment in metastatic colorectal cancer, demonstrating survival benefit and acceptable toxicity profile in the phase III RECOURSE study[1,2] . **Methods:** We performed an updated multicentre retrospective observational study of patients with metastatic colorectal cancer receiving TAS-102 as third line treatment between 2016 and 2019 in 8 cancer centers across the UK. Medical records were reviewed for clinicopathological characteristics, treatment, survival and toxicity outcomes. Prognostic and predictive factors were identified with uni-and multivariate regression analyses. **Results:** A total of 236 patients were included. Median age was 69 years (31-89). All patients had received at least 2 lines of fluoropyrimidine-based chemotherapy doublet with oxaliplatin or irinotecan. About 10% of patients had ECOG ≥ 2. Median duration of TAS-102 treatment was 3 months (0.2-25.9), with an ORR of 2.1% and disease control rate of 21.6%. Median OS was 7.6 months (95%CI 6.5-8.6) and median PFS 3.3 months (95%CI 3.01-3.57). A dose reduction was required in 27% of patients, while 7.6% discontinued treatment due to toxicity. Neutropenia was present in 59%, (≥G3 34%) with 4.6% cases of neutropaenic fever. Thrombocytopenia was less frequent 11% (≥G3 1.6%). Fatigue was reported in 67.3% (G3 9%), nausea 30% (G3 3.3%) and diarrhoea 24.5% (G3 2%). Baseline Neutrophil to Lymphocyte ratio (NLR) <5 and CEA <200 had favourable prognostic (HR: 0.52 and 0.39, p≤0.001) and predictive value (OR: 5.94 and 5.08, p<0.05). Development of G3 neutropenia during treatment predicted treatment response (OR: 3.08, p<0.001) and better OS (HR: 0.44, p<0.001). Following TAS-102 treatment 41% were referred for Phase I trial or re-challenged with chemotherapy. **Conclusions:** These results are consistent with the efficacy and toxicity outcomes from RECOURSE study. However, lower disease control rates and higher rates of dose reductions are seen in the real-world population. Pre-treatment NLR and CEA could serve as potential markers for patient selection. Prospective validation is needed.

OBJECTIVES

To assess efficacy and adverse event profile of TAS 102 in clinical practice in comparison to RECOURSE trial and identify predictors of response.

METHODS

- Retrospective observational study using patient medical records.
- Data were collected on patient demographics, ECOG performance status, site of disease, presence of KRAS mutation, previous treatment, toxicities and treatment outcomes associated with Trifluridine/Tipiracil.
- Patients with metastatic colorectal cancer receiving TAS-102 as 3rd line between January 2016 and January 2019 in eight Cancer centers across the UK:
  - Guy's and St Thomas' NHS Foundation Trust
  - University College London Cancer Institute
  - Maidstone and Tunbridge Wells NHS Trust
  - Beatson West of Scotland Cancer Centre
  - Southampton General Hospital
  - Leicester Royal infirmary
  - Poole Hospital NHS Foundation Trust
  - Queen's Hospital Essex

RESULTS

Table 1. Patient Characteristics

Characteristic	N =236
Age – years /no (%)	
Median	70
< 65	85 (36)
≥ 65	156 (64)
Sex - no (%)	
Male	158 (67)
Female	101 (43)
ECOG PS - no (%)	
0	48 (20)
1	165 (70)
2	23 (10)
Time from diagnosis of metastases- no (%)	
<18 months	159 (32)
≥18 months	74 (68)
Primary site of disease - no (%)	
Colon	159 (67)
Rectum	77 (33)
KRAS mutation - no (%)	
Yes	80 (34)
No	114 (48)
Unknown	42 (18)
Metastatic sites - no (%)	
1-2	97 (42)
≥3	139 (58)
Previous chemotherapy - no (%)	
Fluoropyrimidine doublet*	236 (100)
Bevacizumab	50 (21)
anti-EGFR	83 (35)
Regorafenib	1 (0.4)

Table 2. Predictors of response to TAS-102

Variable	Univariate Model		Multivariate Model	
	OR (95% CI)	p	OR (95% CI)	p
Age <65/ ≥65	1.32 (0.67 – 2.59)	0.40	-	-
Alb <35 / ≥35	0.47 (0.18 – 1.12)	0.12	-	-
PS ≤1/ >1	2.01 (0.57 – 7.2)	0.26	-	-
NLR<5/ ≥5	5.94 (1.67 – 19.3)	0.005*	3.49 (0.97 -12.5)	0.05*
PLR <300/ ≥300	2.54 (0.84 – 7.6)	0.09	-	-
CEA <200/ ≥200	5.08 (2.31 – 11.1)	<0.001*	6 (2.23 -16.6)	<0.001*
Neutropaenia ≥G3/ <G3	3.08 (1.58 – 5.9)	0.001*	2.1 (1.02 – 4.4)	0.04*
Met sites ≤1/ >1	1.028 (0.54 – 1.9)	0.9	-	-
Right/ Left tumour	1.119 (0.17 – 2.17)	0.73		

Abbreviations: Alb; Albumin, NLR; Neutrophil to Lymphocyte ratio, PLR; Platelet to Lymphocyte ratio, PS; Performance status. Met; metastatic

Figure 1. Treatment induced neutropaenia predicts overall survival

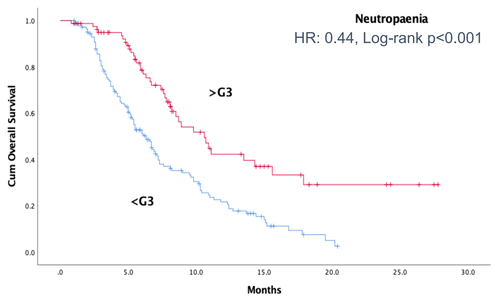


Table 3.Comparative analysis of treatment outcomes

Outcome	Our Study	RECOURSE[1]
Median treatment duration-months (range)	3 (0.2 – 25.2)	1.67 (0.3-19.5)
ORR	2.1%	1.6%
Disease control	21.6%	44%
Median OS- months (95% CI)	7.6 (6.5 – 8.6)	7.1 (6.5 – 7.8)
Median PFS-months (95% CI)	3.3 (3.02 – 3.57)	2 (1.9 – 2.1)

Figure 2: Treatments following Trifluridine/Tipiracil

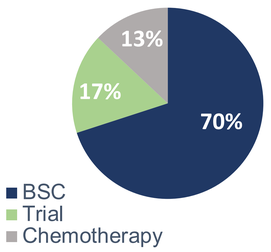
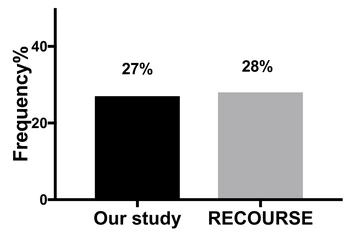


Table 4. Adverse events in patients treated with TAS-102 : comparison with RECOURSE study

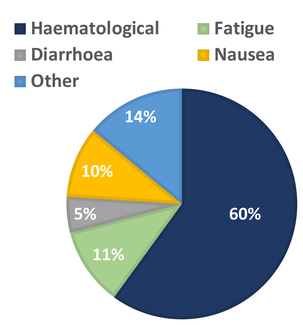
Adverse event – no (%)	Our study (N=236)		RECOURSE[1] (N=534)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	159 (67%)	22 (9%)	188 (35%)	21 (4%)
Neutropaenia	139 (59%)	82 (35%)	353 (67%)	200 (38%)
Nausea & vomiting	72 (30%)	8 (3%)	406 (76%)	21 (4%)
Diarrhoea	58 (24.5%)	5 (2%)	170 (32%)	16 (3%)
Thrombocytopaenia	27 (11%)	4 (1.6%)	223 (42%)	27 (5%)
Febrile neutropaenia	11 (4.6%)	-	20 (4%)	

Figure 3. Dose reductions in patients receiving TAS-102



Of those who had a DR	RECOURSE[1]
1 DR 89%	72%
2 DRs 11%	25%
3 DRs 0	3%

Figure 4. Reasons for dose reductions in our study population



CONCLUSIONS

- OS, PFS and ORR observed in our real-world experience were consistent with the RECOURSE trial though we noted a lower disease control rate.
- Overall, TAS-102 was well tolerated and the most prevalent adverse events seen in our patients were in keeping with those reported in the trial (haematological and GI toxicities).
- Pre treatment Neutrophil to Lymphocyte ratio (NLR) <5 and CEA <200 had a favourable prognostic and predictive value.
- Development of G3 neutropenia during treatment predicted treatment response and better survival outcomes.

REFERENCES

1. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909–1919
2. Eric Van Cutsem ,Alfredo Falcone, Rocio Garcia-Carbonero, et al. Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. ESMO Open 2017 Nov 23;2(5):e000261

Email: chara.stavraka@kcl.ac.uk