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TAS-102 Plus Bevacizumab as an Effective and Well Tolerated Regimen in Chemotherapy-Refractory Advanced Colorectal Cancers – A Single Institution Retrospective Analysis

Ritam Joarder[1] Dhwani Patel[1] Atul Tiwari[1] Jatin Choudhary[1] Pranaya Vana[1] Vallish Shenoy[1] Neha Mer[1] Anant Ramaswamy[1] Prabhat Bhargava[1] Vikas Ostwal[1]

[1] Department of Medical Oncology, Tata Memorial Hospital, HBNI, Dr. E Borges Road, Parel, Mumbai, India

Address for correspondence Vikas Ostwal, DM, Professor, Department of Medical Oncology, Tata Memorial Hospital, HBNI, Dr. E Borges Road, Parel, Mumbai 400012, India (e-mail: dr.vikas.ostwal@gmail.com).

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Abstract

Ritam Joarder

Objective There are limited data on the utility of TAS-102 plus bevacizumab in patients with chemotherapy-refractory metastatic colorectal cancer (mCRC) treated in India.

Methods Patients diagnosed with chemotherapy-refractory mCRC, defined as having received at least prior oxaliplatin and irinotecan–based chemotherapy between January 2017 and January 2022, and who began treatment with a combination of TAS-102 and bevacizumab were retrospectively analyzed for demographic variables, survivals, and prognostic parameters. The primary endpoint of the study was estimation of the median overall survival (OS) by the Kaplan–Meier method.

Results The data of 143 patients satisfied the prespecified inclusion criteria and were included for analysis. There was a predominance of left-sided CRCs (78%) and patients having greater than two sites of distant metastases (87%), with 41% of patients with at least two lines of prior therapy. With a median follow-up of 11.6 months, the median OS of the entire cohort was 10.9 months, while the median progression-free survival was 4.4 months. The combination was well tolerated, with the most common grade 3/4 side effects being neutropenia (25%), anemia (6%), and thrombocytopenia (4%). Dose modifications in TAS-102 were required in 20% of patients, though this did not entail permanent cessation of TAS-102 in any patient. The presence of a resected primary was prognostic for improved OS ($p < 0.001$), while signet ring histology predicted inferior OS ($p < 0.001$).

Conclusion The combination of TAS-102 and bevacizumab is an efficacious and safe therapeutic option in patients with mCRC who have received at least two lines of prior systemic therapy. There were no requirements for cessation of the combination in the current study, underlying the well-tolerated nature of the combination.

Keywords

- bevacizumab
- chemotherapy-refractory colorectal cancer
- TAS-102
- tipiracil
- trifluridine

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Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality across the world.[1] In India, CRCs accounts for approximately 4.9% of all new cancer patients and is responsible for about 4.5% of all cancer-related deaths in the country.[2,3] Limited evidence suggests that a greater proportion of CRCs present as advanced or metastatic CRCs (mCRC; 28%) in India as compared to the United States and Europe (15–20%).[4]

The backbone of the management of advanced or mCRC is chemotherapy (predominantly 5-fluorouracil [5-FU] or oral analogues of 5-FU, irinotecan, and oxaliplatin), anti-vascular endothelial growth factor (anti-VEGF) inhibitors, and epidermal growth factor receptor (EGFR) inhibitors where indicated.[5–7] A small proportion of patients (5%) are treated with immune checkpoint inhibitors (ICIs) for microsatellite instability (MSI) mCRC.[8,9]

However, a majority of patients with mCRC eventually have disease progression or loss of response to oxaliplatin and irinotecan–based therapies and are labeled as "chemotherapy-refractory" mCRC. Well-validated options in this scenario include TAS-102 (trifluridine–tipiracil) alone or with bevacizumab, regorafenib, and fruiquitinib.[10–14] TAS-102 is an orally active drug composed of a thymidine analog (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). In this study, we evaluated the efficacy and safety of TAS plus bevacizumab in patients with mCRC refractory to oxaliplatin and irinotecan–based chemotherapy.

Methods

Patient Selection

The current retrospective study aimed to evaluate the survivals of patients with mCRC who were considered chemotherapy refractory. The investigators evaluated data from a prospectively maintained CRC database at the Tata Memorial Hospital (TMH) and included patients who had been treated between January 2017 and January 2022. Patients included in the study satisfied the following criteria: histologically confirmed adenocarcinoma; radiologically confirmed unresectable or metastatic cancer; prior receipt of oxaliplatin- and irinotecan-based chemotherapy (irrespective of use of targeted therapeutic agents) at least (prior receipt of regorafenib, monotherapy with anti-EGFR-directed therapy as monotherapy was allowed); started on TAS-102 plus bevacizumab and had at least one follow-up visit documenting response postadministration, and had documented dates of starting and cessation of TAS-102 plus bevacizumab.

Clinical Data Collection

Data collected were demographic and clinical variables, disease-specific data including the RAS status, BRAF status, MSI, details of TAS-102 plus bevacizumab administration, adverse events, and oncologic outcomes. The primary endpoint of the study was estimation of the median overall survival (OS), while the secondary endpoints were was estimation of progression-free survival (PFS), overall response rates (ORR), and adverse event rates.

Ethics and Consent

The approval for the study was obtained from the Institutional Ethics Committee at the TMH (IEC418). The approval included the requirement of a short telephonic consent for patient data accrued at the TMH as part of ethics committee requirements. Data collection and handling were conducted as per the ethical guidelines of the declaration of Helsinki.

Statistics

Data were analyzed using IBM SPSS version 20 (Armonk, NY, United States). Descriptive statistics such as median, frequency, and percentage were used to summarize the categorical variables. The primary endpoint of the study was estimation of the median OS, which was calculated from the date of starting TAS-102 and bevacizumab to the date of death or loss of follow-up, whichever was earlier. Secondary endpoints were PFS, which was calculated from the date of diagnosis of starting TAS-102 and bevacizumab to the date of progression, loss to follow-up, or death, whichever was earlier, and overall response rates (ORR), which were calculated by combining the complete response (CR) and partial response (PR) rates, while the clinical benefit rate (CBR) was reported as a summation of the CR, PR, and stable disease (SD) rates. Grade 3 and 4 toxicities were recovered from medical records and reported as per the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0. Survival analysis was performed using the Kaplan–Meier estimates, and the log-rank test was used for bivariate comparisons. Select prognostic factors were evaluated and those with a p-value of ≤ 0.05 on univariate analysis were considered significant.

Result

Baseline characteristics

A total of 143 patients satisfying the inclusion criteria were included in the study. Briefly, the median age of the patients was 52 years (range: 14–77 years); the majority of patients were Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 (92%) and had left-sided primary CRC (78%) and 17% of the patients had signet ring histology. A detailed representation of the baseline characteristics is presented in ►Table 1.

Delivery of TAS-102 and Bevacizumab and Treatment-Related Adverse Events

Most patients (92%) were started on full dose of TAS-102 and bevacizumab. Dose modifications in TAS-102 were required in 29 patients (20%), with the most reasons for dose modifications being grade 3 and 4 hematological toxicities. No dose reductions in bevacizumab were required or made. Overall, the most common grade 3 and 4 treatment-related

Table 1 Baseline demographic and preclinical characteristics

Characteristics	Number (%)
Median age (y)	52 (range: 14–77)
Sex Male Female	106 (74) 37 (26)
ECOG performance status 0–1 2 3	132 (92) 10 (7) 1 (1)
Primary tumor location Right side colon Left side colon Rectum	31 (22) 35 (24) 77 (54)
Histology MDAC PDAC None	82 (58) 40 (28) 21 (15)
Signet histology Yes No	24 (17) 119 (83)
No. of metastatic sites <2 ≥2	19 (13) 124 (87)
Site of metastatic disease Liver Lung Lymph nodes Peritoneum Bone	73 (51) 23 (16) 8 (6) 37 (26) 2 (1)
RAS mutation status Wild type Mutant Unknown	59 (41) 37 (26) 47 (33)
BRAF mutation status Wild type Mutant Unknown	96 (77) 0 (0) 47 (33)
MMR status Deficient Proficient Not available	0 (0) 113 (79) 40 (21)
Previous lines of therapy ≤2 >2	84 (59) 59 (41)
Resection of primary Yes No	81 (57) 62 (43)
Previous bevacizumab treatment No Yes	48 (33) 95 (67)
Previous regorafenib treatment No Yes	125 (87) 18 (13)

Abbreviations: ECOG, eastern cooperative oncology group; MDAC, moderately differentiated adenocarcinoma; MMR, Mismatch repair; PDAC, poorly differentiated adenocarcinoma; RAS, rat sarcoma virus.

Table 2 Treatment-related adverse events (TRAE)

TRAE	Grade 1–2	Grade 3-4
Anemia	92 (64)	14 (10)
Neutropenia	62 (43)	35 (25)
Thrombocytopenia	53 (37)	16 (11)
CINV	47 (33)	2 (1)
Diarrhea	34 (24)	5 (4)
Fatigue	48 (34)	–
Mucositis	11(8)	–
Hypertension	4 (3)	–
Bleeding	1 (1)	–

adverse events (TRAEs) were neutropenia (25%), thrombocytopenia (11%), and anemia (10%; ►**Table 2**).

Response Rates, Survival, and Prognostic Factors

All patients had data available for response rates. Ten patients had a PR (7%), while 68 patients (48%) had SD as the best response to treatment. CBR for the overall cohort was 55%.

With a median follow-up of 11.6 months (95% confidence interval [CI]: 9.66–13.54), the median OS of the entire was 10.9 months (95% CI: 8.9–12.8) in the current study (►**Fig. 1**). At the time of data analysis, 108 patients had disease progression (75%) and the median PFS for the entire cohort was 4.4 months (95% CI: 3.1–5.7). Of the factors evaluated as prognostic for OS, the presence of prior resection of the primary tumor predicted for improved OS, while signet ring histology predicted for inferior OS with TAS-102 and bevacizumab (►**Supplementary Table S1**, available online only).

Discussion

The current study highlights the clinical utility and safety of the combination of TAS-102 and bevacizumab in chemotherapy-refractory advanced CRC and is the first report on this combination from the Indian scenario.

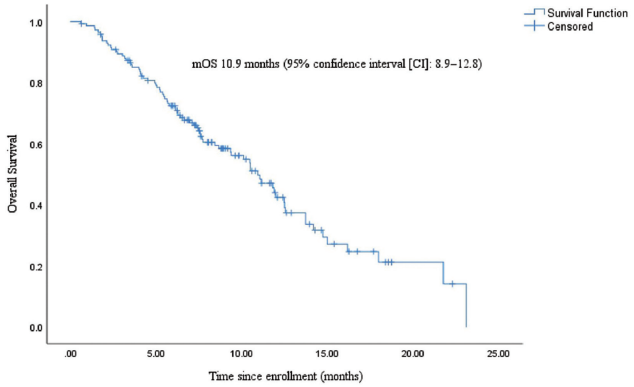

Fig. 1 Overall survival. mOS, median overall survival.

There are limited efficacious treatment options for patients refractory to oxaliplatin and irinotecan–based therapy. The RECOURSE trial (comparing TAS-102 with placebo), the SUNLIGHT trial (comparing TAS-102 plus bevacizumab with TAS-102 alone), and other studies have clearly showed that TAS-102 with or without bevacizumab showed modest but relevant improvements in OS.[10,12,15,16] The clinical profile of patients in this study has certain notable characteristics—17% of patients had signet ring histology, almost 60% of patients had greater than two sites of metastases, more than 40% of patients had received more than two lines of prior therapy, and a minority of patients had received prior regorafenib as well (13%). Despite these characteristics, the response rates and survivals of patients in this study is encouraging and on par with published trials and real-world evidence from other countries.[17,18] As expected, most patients had disease stabilization as their best response to therapy. A majority of studies have shown median survivals upward of 10 months and the current study has shown similar outcomes. More importantly, it was a well-tolerated regimen with no requirements for drug cessation due to TRAEs. The well-tolerated nature of this regimen has led to its use in potentially frail patients with advanced CRC unsuitable for intensive systemic therapy.[19]

Two important points were noted in this study—the negative prognosis associated with signet ring histology and the improved outcomes in patients with resected tumors. Multiple previous datasets from India have shown that signet ring histology is a negative prognostic factor and further research is needed to delve into the biology of these aggressive tumors.[5,20,21] With regard to resection of the primary tumor conferring a survival advantage, a phase 3 trial from Japan has clearly shown the futility of primary tumor resections in patients with advanced mCRC.[22,23]

The current study has caveats that need to be acknowledged. It evaluates a small cohort of patients retrospectively from a single institution and this limits the generalizability of the results. We have limited data on further treatment options offered to patients who had disease progression on TAS-102 plus bevacizumab.

In conclusion, the combination of TAS-102 and bevacizumab is an efficacious and safe therapeutic option in patients who have received at least two lines of prior systemic therapy (chemotherapy refractory). There were no requirements for cessation of the combination in the current study, underlying the well-tolerated nature of the combination.

Conflict of Interest

None declared.

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