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ORIGINAL RESEARCH

TAS-102 in metastatic colorectal cancer (mCRC): efficacy, tolerability, and quality of life in heavily pretreated elderly patients: a real-life study

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Abstract

Background: TAS-102 is an oral monotherapy, combining trifluridine and tipiracil hydrochloride, indicated for the treatment of pretreated metastatic colorectal cancer (mCRC). The aim of this real-life study is to evaluate the efficacy and safety of TAS-102 in heavily pretreated elderly patients with mCRC whose disease has progressed with standard therapies.

Methods: In this retrospective observational study, we enrolled 50 elderly patients >70 years of age (median age 78 years) with a diagnosis of mCRC who were previously treated or were not considered candidates for treatment with other available therapies. Patients aged >70 years with advanced colorectal cancer and with an ECOG performance status of grade 0 (*n*=18) or grade 1 (*n*=32) were included. Overall survival and progression-free survival were the primary endpoints, whereas objective response rate, tolerability, and quality of life were the secondary endpoints.

Results: Treatment with TAS-102 appeared to be well tolerated and side effects were generally mild, achieving disease control and a benefit on quality of life. The median overall survival was 6.7 (95% CI 5.7–11.3) and the median progression-free survival was 2.1 months (95% CI 1.2–3.2), estimated using the Kaplan–Meier method.

Conclusion: TAS-102 represents a manageable and effective therapeutic opportunity and appeared to be well tolerated with generally mild side effects in elderly patients with mCRC who were heavily pretreated with standard therapies.

Keywords: chemotherapy, elderly patients, Lonsurf, metastatic colorectal cancer, quality of life, TAS-102, trifluridine/tipiracil.

Citation

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Introduction

Colorectal cancer (CRC) represents the second most common malignancy by incidence in western countries after breast cancer in women and prostate cancer in men. Although the prognosis linked to CRC has improved in recent years, mortality remains high, especially for refractory or metastatic CRC (mCRC). Indeed, mCRC is a major cause of death from malignant neoplasm.[1] Approximately 20% of patients with CRC have clinically detectable liver metastases at initial diagnosis and approximately 45% develop metastases during the course of the disease.[2,3] A multidisciplinary group approach represents the best path for the correct management of patients with mCRC. The introduction of new drugs into clinical practice has progressively improved survival in advanced disease, bringing the median survival to 24 months; furthermore, in some cases, new drugs have allowed the conversion of advanced disease from unresectable to surgically resectable.[4,5]

In heavily pretreated patients and in elderly patients >70 years of age, the goal of systemic treatment is to improve quality of life (QoL), prolong survival, and to postpone the onset of complications related to the disease. TAS-102 (Lonsurf®) is an oral monotherapy that combines trifluridine (FTD) and tipiracil hydrochloride (a thymidine phosphorylase inhibitor) and is indicated for the treatment of mCRC in heavily pretreated patients.[6] FTD acts by incorporation into DNA, resulting in cell cycle arrest and cell death,[7] whereas tipiracil hydrochloride

maintains adequate plasma concentrations of FTD by inhibiting thymidine phosphorylase, which degrades FTD.[5] In the phase III RECOURSE study, TAS-102 demonstrated an improvement in overall survival (OS) from 5.3 to 7.1 months and in progression-free survival (PFS) from 1.7 to 2.0 months, without significant adverse effects and with a good safety profile in heavily pretreated patients.[8] Furthermore, an analysis of the subgroups of the RECOURSE study highlighted the benefits of TAS-102 treatment in elderly patients.[9] Age does not affect the efficacy of TAS-102 and does not represent a potential risk factor for toxicity. Therefore, age alone should not preclude the use of TAS-102 in patients aged >70 years.[10, 11] However, despite the high incidence of this disease in elderly patients, the available clinical practice information regarding this population is limited and incomplete. Based on the results of the RECOURSE subgroups as well as on studies by Van Cutsem et al.[8] and others,[9,12,13] we conducted a study to evaluate the safety and efficacy of TAS-102 in heavily pretreated elderly patients with mCRC.

Materials and methods

Study design

This observational retrospective study was conducted to evaluate the safety and efficacy of TAS-102 monotherapy in mCRC in elderly patients treated at the Oncology Unit of the University of Palermo. The patients enrolled in this study had previously been treated with or were refractory to standard therapies, including oxaliplatin, irinotecan, 5-fluorouracil, capecitabine, anti-VEGF drugs, and anti-EGFR drugs. No patients had previously been treated with regorafenib. OS and PFS were the primary endpoints, whereas objective response rate (ORR), tolerability, and QoL were the secondary endpoints. The study was approved by the Ethics Committee of Policlinic Palermo, Italy, in the January 2014 session. Consent from the patients was obtained to review their medical records. The study was conducted in accordance with the provisions of the Declaration of Helsinki and good clinical practice guidelines and all patients enrolled provided written informed consent to be treated with TAS, for data storage, and for future analysis and publication of the data.

Patient selection

This retrospective observational study was conducted between March 2014 and June 2019 and involved the treatment of a total of 50 patients aged >70 years and with a mCRC diagnosis refractory or intolerant to standard therapies; all patients were treated with TAS-102 (see Modality of administration section) in our Institution. All patients were judged not to be amenable to regorafenib treatment due to poor clinical conditions. To be eligible for inclusion, all patients must have received approved conventional therapies and documented disease progression. Furthermore, all patients evaluated had to meet the following inclusion criteria: (1) colorectal carcinoma, histologically or cytologically confirmed, with measurable or evaluable disease; (2) unresectable stage IV carcinoma pretreated with conventional therapies; (3) age over 70 years; (4) life expectancy >3 months; (5) regular cardiac function with left ventricular ejection fraction at rest >50% and sinus rhythm on the electrocardiogram; (6) performance score status between grades 0 and 1 according to the Eastern Cooperative Oncology Group (ECOG); (7) clinical or radiological evidence of metastatic measurable disease by spiral computer tomography (CT) scan or magnetic resonance imaging scan, in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, with ≥1 lesions; and (8) the required laboratory results (neutrophils 2.0×10^9/L, platelets 100×10^9/L, hemoglobin 10 g/dL, creatinine 1 mg/dL, the upper limit of the standard (ULN), creatinine clearance >60 mL/min if creatinine was above the indicated limit, bilirubin 1×ULN, aspartate aminotransferase and alanine aminotransaminase 5×ULN, and alkaline phosphatase 5×ULN; except in the presence of bone metastases). Patients with asymptomatic central nervous system metastases were included in the study provided that surgical or radiotherapy treatment was completed no more than 3 months prior. Patients were excluded from the study if they (1) were hypersensitive to TAS-102 and its excipients or other components of the formulation; (2) had a diagnosis of other malignant tumors except for adequately treated basal cell carcinoma of the skin; (3) had clinically active cardiovascular disease, myocardial infarction in the 6 months prior to enrollment in the study, or severe cardiac arrhythmia; (4) had symptomatic brain metastases; or (5) had severe comorbidity not adequately controlled by other ongoing therapies (liver disease, diabetes, infections, heart disease, etc.).

Evaluation of response and toxicity

The evaluation of response rate in terms of measurable pathology reduction, in accordance with RECIST version 1.1,[14] was conducted at the beginning of treatment and every 3 months until disease progression. A spiral CT scan was always performed before the start of treatment and subsequently on average every 3 months or coinciding with the alleged progression. Positron emission tomography was performed in selected cases at the discretion of the physician. In the case of brain metastases, a magnetic resonance imaging scan was performed every 6–12 weeks. Dose interruptions were authorized to manage treatment-related adverse events. Basic laboratory assessments were always performed every 12–14 days and before the next treatment, and safety assessments were made during the treatment phase. Management of hematological toxicity in elderly patients treated with TAS-102 resulted in discontinuation of dosing until the toxicity was resolved by returning the values to at least G1 or baseline. The drug-related toxicities were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment continued until clinical benefit was observed or until treatment was no longer tolerated.

QoL value

QoL was routinely assessed for all patients at the start of treatment and at the first follow-up (3 months) through the administration of the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer)[15] questionnaire by a psycho-oncologist; EORTC QLQ-C30 is composed of both multiitem scales and single-item measures, including five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and six single items (dyspnea, loss of appetite, insomnia, constipation, diarrhea, and perceived financial impact of the disease). A higher scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Modality of administration

Considering a 28-day cycle, TAS-102 was administered orally twice a day for 5 days, followed by a 2-day break, repeated for 2 weeks, with a subsequent 14-day break period. The recommended starting dose was 35 mg/m^2, administered orally twice daily and doses not taken, either because they were forgotten or suspended, did not have to be compensated. Dose reductions were anticipated (up to a maximum of three reductions) in case of additional toxicity. Before resuming treatment, the dose had to be reduced by 5 mg/m^2 compared to the previous dosage. These reductions were allowed up to a minimum dose of 20 mg/m^2 twice daily. Adherence was assessed using the medication possession ratio and the proportion of days covered at 3 months. In addition, during the entire treatment period, the patient was advised to maintain adequate hydration to prevent complications such as kidney failure. Treatment was administered until progression, unacceptable toxicity, or patient rejection. According to clinical practice procedures, therapy was postponed for up to 2 weeks if the neutrophil count was <1.5×10^9/L or if the platelet count was <100×10^9/L, if the hemoglobin level was <8.5 g/dl, or if bilirubin and/or transaminase levels were >1.5×ULN. In the case of neutropenia (grade 2–3) granulocyte colony-stimulating factor (G-CSF) was subcutaneously administered as prophylaxis. In case of severe anemia (grade 4), blood transfusions were performed, whereas erythropoietin ampoules were administered subcutaneously in less severe cases. Finally, platelet infusions were administered intravenously in cases of severe thrombocytopenia (grade 4). Progressing patients were assigned to begin a new treatment.

Statistical analysis

The analyses were performed using statistical software SPSS (Statistical Package for Social Science) version 25.0 for Mac (IBM Corp.). Descriptive statistical analysis was performed to provide a sociodemographic representation of the group of participants in the study and to explore how the analyzed variables were distributed. The normality of distribution was verified through univariate kurtosis and asymmetry indices with an acceptance threshold of 1. No variance violated the normality indices. Inferential statistical analyses were performed to detect the existence of significant associations between the variables considered. The disease control rate was defined as the percentage of patients with an objective response and/or stable disease lasting >6 months. PFS and OS were calculated from the date of the beginning of treatment until the date of disease progression or death from any cause for PFS and until the date of the last follow-up, death, or final follow-up day of evaluation for OS. PFS and OS curves were estimated using the Kaplan–Meier method. The last follow-up was in December 2019. In addition, the Bravais–Pearson (r) linear correlation index was used to measure the intensity of the bond between the OS variable and QoL with a 95% confidence interval (CI). Considering the sample amplitude, parametric statistics were used and a threshold value of 0.05 was considered to evaluate the significance of the data obtained.

Results

Patient characteristics

The retrospective analysis was performed by including 50 nonconsecutive patients (28 men and 22 women), with an average age of 78 years (range 70–86). All patients underwent primary tumor surgery, and all patients had previously undergone conventional therapies such as oxaliplatin, irinotecan, 5-fluorouracil, capecitabine, anti-VEGF, and anti-EGFR in patients with wild-type *RAS*, but none had any prior treatment with regorafenib. Following biomolecular investigations, 32 patients were shown to have mutant *KRAS* tumors and 18 patients had wild-type *KRAS*. Only 12 patients were evaluated for *BRAF* status. A total of 18 patients had an ECOG performance status of grade 0 and 32 had an ECOG performance status of grade 1. Patients with an ECOG performance status of grade 2 were excluded from the study. The sites of disease at the last radiological investigation were the liver, lungs, and peritoneum (Table 1). Heart failure or left ventricular ejection fraction did not occur in any patient. During the study period, in our center, 52 patients were treated with regorafenib whereas 32 received supportive therapy alone.

OS and PFS analysis

Among the 50 patients enrolled in this study, the updated interim analysis of survival showed a median OS of 6.7 months (95% CI 5.7–11.3) (Figure 1). Median PFS was 2.1 months (95% CI 1.2–3.2) (Figure 2).

Table 1. Baseline demographic and clinical characteristics (*n*=50).

Characteristics	Patients, % (*n*)
Mean age, years (range)	78 (70–86)
Gender	
Male	56% (28)
Female	44% (22)
ECOG performance status	
0	36% (18)
1	64% (32)
Primary tumor location	
Single left site	48% (24)
Single right site	24% (12)
Single transverse site	8% (4)
Single rectum site	20% (10)
KRAS status	
Wild type	28% (14)
Mutated	52% (26)
BRAF status	
Wild type	76% (38)
Mutated	24% (12)
Location of metastasis	
Liver	32% (16)
Lung	16% (8)
Peritoneum	52% (26)
Other	12% (6)

ECOG, Eastern Cooperative Oncology Group.

Figure 1. Kaplan–Meier plot of median overall survival (mOS) (*n*=50).

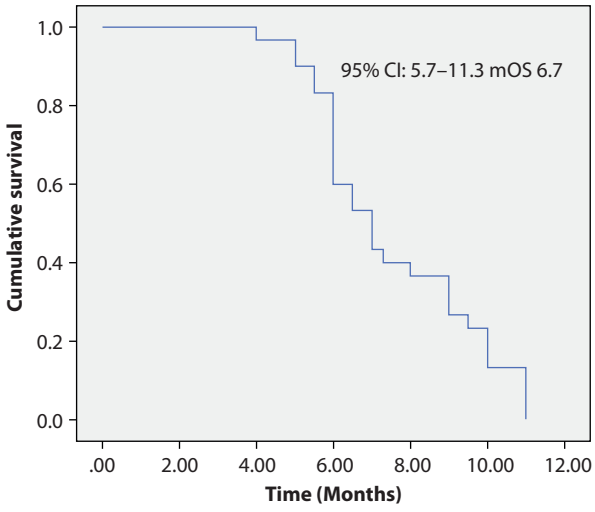
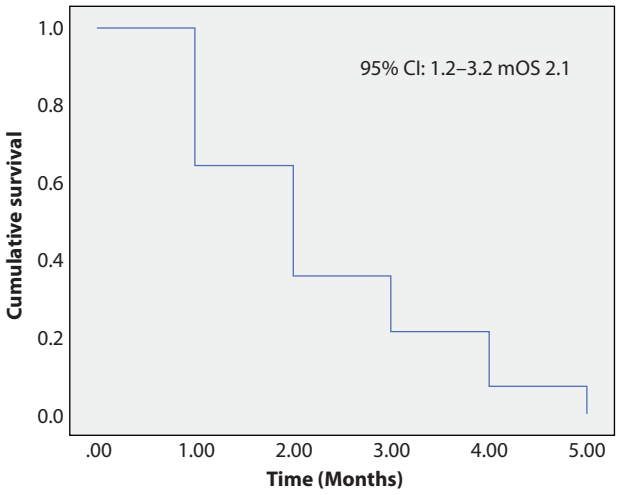


Figure 2. Kaplan–Meier plot of progression-free survival (mPFS) (*n*=50).



ORR analysis

Treatment with TAS-102 showed a good level of disease control with a manageable toxicity profile. No partial or complete responses were reported (ORR 0%). The first instrumental re-evaluation with spiral CT was performed after 3 months of treatment. Two patients did not undergo disease reassessment: one patient died after the first cycle and one patient was soon lost to follow-up due to complications. The overall ORR was 0%, disease stabilization 58%, disease progression was 38%, and 4% were not evaluable (Table 2). The mean duration of follow-up was of 6.1 months (range 3–9.2 months), and the median response time was 9.2 weeks (95% CI 6.7–12.2 weeks) with a significant impact on the QoL. The bimolecular evaluation of tumor mutation status compared to *KRAS* showed that the benefits of TAS-102 treatment were observed in both tumor mutation patient subgroups without statistical differences. In the 18 patients with a *BRAF* mutational status, TAS-102 also showed a benefit. The treatment showed a good level of disease control with no objective response; therefore, TAS-102 was associated with stable disease with a manageable toxicity profile in heavily pretreated elderly patients with mCRC.

QoL analysis

QoL was measured with EORTC QOL-C30 (ref.[15]) and was analyzed as a change from baseline at follow-up with a score of 49.6 (0–100) in the global health status/QoL scales. The QoL showed an improvement with treatment in 58% of patients. Scores on the functional scales of the EORTC QLQ-C30 varied, indicating that the patients' QoL was sufficient overall. An improvement in QoL was also identified with a reduction in pain symptoms, with a score of 33.5, and an improvement in physical functioning (score 39.6), role functioning (score 42.4), constipation (score 23.6), fatigue (score 24.1), and appetite

Table 2. Overall response rate (*n*=50).

Best response	Investigator assessment (%)
Complete response	(0)
Partial response	(0)
Stable response	(58)
Progressive response	(38)
Not evaluable	(4)
Overall response rate (CR+PR)	(0)
Clinical benefit rate (CR+PR+SD)	(52)

CR, complete response; PR, partial response; SD, stable response.

loss (score 23.1). Moreover, the Bravais–Pearson index showed a positive correlation between the response rate of OS and QoL, with a value of 0.58 (95% CI 0.24–0.79; p=0.006). The compliance with TAS-102 treatment was assessed by a monthly telephone interview with patients and at least one of their family members by a psycho-oncologist.

Safety and adverse events

A total of 380 therapy cycles were performed, with each patient undergoing 7.6 cycles on average. The duration of treatment in one patient reached 14 months. Treatment-related toxicity was well tolerated and adverse events were assessed after each cycle of therapy and reported in line with CTCAE version 4.0. No patient died from treatment-related adverse events. Most adverse reactions related to TAS-102 therapy were resolved with the application of established safety guidelines. The hematological toxicity was the most frequent complication; 13 (26%) patients developed grade 3–4 neutropenia, which required the use of G-CSF as prophylaxis; 8 (16%) patients developed febrile neutropenia, which required the use of antibiotics and G-CSF; 2 (4%) patients developed grade 2 thrombocytopenia, which required the use of corticosteroids; and 4 (8%) patients developed grade 3 anemia, which required the administration of subcutaneous erythropoietin. All toxicity effects were managed by dose modification and delayed administration. Due to deteriorating clinical conditions, advanced age, and comorbidities, one patient stopped treatment after three administrations. An episode of grade 4 febrile neutropenia occurred in three patients at the end of the first cycle on day 27, which caused a delay of 6 days at the beginning of the second cycle and was treated with antibiotic therapy and subcutaneous G-CSF as prophylaxis. Treatment continued without a dose reduction. During the fourth cycle, two other patients experienced a febrile episode of grade 4 neutropenia that caused treatment to stop for 8 days and prophylaxis with subcutaneous G-CSG was administered with blood chemistry monitoring. Considering the suspension of therapy for more than a week, the dose was reduced to

Table 3. Adverse events graded according CTCAE, Version 4.0 (*n*=50).

Adverse events	All grades, % (*n*)	Grade 3–4, % (*n*)
Hematological		
Anemia	18% (9)	8% (4)
Neutropenia	36% (18)	26% (13)
Thrombocytopenia	4% (2)	0% (–)
Febrile neutropenia	16% (8)	16% (8)
Nonhematological		
Nausea	16% (8)	0% (–)
Vomiting	8% (4)	2% (1)
Constipation	0% (–)	0% (–)
Fatigue	18% (9)	4% (2)
Hyperbilirubinemia	8% (4)	2% (1)
Hand–foot syndrome	10% (5)	4% (2)
Peripheral neuropathy	0% (–)	0% (–)
Diarrhea	12% (6)	2% (1)

CTCAE, Common Terminology Criteria for Adverse Events.

30 mg/m^2 bid and the patients continued without significant disturbances and good hematological tolerance. Other common adverse events included fatigue (6%), grade 3 nausea (6%), vomiting (6%), diarrhea (4%), hand–foot syndrome (4%), and hyperbilirubinemia (2%) (Table 3). All adverse events were managed, generally on an outpatient basis, with adequate intervention of supportive therapies and with a reduction or postponing of subsequent administration in line with the TAS-102 guidelines. Dose reduction and dose interruptions were authorized to manage treatment-related adverse events. The dose was reduced in three patients due to toxicity yet it was not postponed in any patient. Four patients underwent thermal ablation on liver metastases. Treatment continued until clinical benefit was observed or until treatment was no longer tolerated.

Discussion

The incidence of tumors increases significantly with age, with a subsequent increase in the incidence of CRC in the elderly. In 2019, 24% of newly diagnosed CRC patients were aged >70 years[16] and 14% of CRC deaths are expected to occur in these patients in the coming years.[17,18] In elderly patients with mCRC, the goal of treatment includes the control of symptoms, maintaining good QoL, and increasing survival. Despite the rapid growth in the number of onco-geriatric patients, elderly cancer patients are underrepresented in clinical trials and the results of clinical trials in younger patients cannot be extrapolated to the treatment of the

elderly. Indeed, the effects of drug toxicity on older people are different than in younger patients. While the adverse events of grade 2 are not important in young people and are often not reported, the same level of toxicity can lead to a significant deterioration of functionality in elderly patients. In this real-life study, we demonstrated that TAS-102 has definite activity with a manageable toxicity profile in elderly patients with mCRC refractory to standard chemotherapy. In our study, TAS-102 demonstrated a median OS of 6.7 months and a median PFS of 2.1 months, in line with reported data.[19,20] Our data confirm previous results that show that treatment with FTD/tipiracil in daily clinical practice is feasible and safe. In an analysis carried out on 136 patients from different Dutch centers, TAS-102 treatment achieved median PFS and median OS of 2.1 (95% CI 1.8–2.3) and 5.4 months (95% CI, 4.0–6.9), respectively.[21] Cardiotoxicity in the form of cardiac arrhythmia, myocardial infarction, and angina-like symptoms or common complications of fluoropyrimidines (such as 5-fluorouracil and capecitabine) did not occur in any patient in this study. TAS-102 is a drug of choice for heavily pretreated elderly patients with advanced CRC who suffer from heart problems during treatment with 5-fluorouracil or capecitabine.[22] Moreover, it appears to be the most available cardio-delicate nucleoside analog in clinical practice and may represent the preferred agent when 5-fluorouracil is indicated.[23] These results reveal that elderly patients can tolerate TAS-102 as well as young patients without frequent interruptions due to adverse events.[24,25] The advantage was evident regardless of the presence or absence of mutations in *KRAS* and *BRAF*.

The elderly patient with cancer is often excluded from clinical studies, making them particularly exposed to the risk of adverse reactions and drug interactions due to their reduced functionality of organs and systems.[26,27] Another very important aspect in clinical studies with elderly patients with cancer is the geriatric assessment, including not only the age but also the functional, social, and mental state of patients. A comprehensive geriatric assessment leads to improved assessment and better determines the individual treatment strategies for optimal outcome. Herein, a comprehensive geriatric assessment was performed in all but 12 patients because an expert geriatrician is not available in our healthcare facility. We assessed cognitive and social function with the administration of the QoL questionnaire by the psycho-oncologist. The psycho-oncologist also assessed treatment compliance and 90% of patients reported taking the drugs as prescribed by the investigator except in the event of interruptions due to toxicity. The collaboration of family members was fundamental in the management of these patients, as shown by the medication possession ratio and proportion of days covered at 3 months. This real-life analysis suggests that TAS-102 monotherapy has a promising activity with manageable safety, suggesting that it could be a potential treatment option for heavily pretreated or refractory elderly patients with all standard therapies in mCRC, according to previous clinical practice studies.[28]

The adverse events among elderly patients in this study were no different from those in younger patients from other studies. Therefore, the therapeutic approach with TAS-102 for heavily pretreated elderly patients with mCRC recalls that of younger patients. Thus, this study suggests that oral monotherapy with TAS-102 can represent one of the emerging therapeutic options in mCRC in pretreated elderly patients aged >70 years, with a favorable risk-to-benefit ratio.[26,29] The results show that TAS-102 is well tolerated and safe in heavily pretreated elderly patients and confirmed that the main benefit is associated with stable disease rather than with tumor reduction, even considering that the objective response to treatment was only observed in a few patients. In addition, an increase in survival curves was also observed. TAS-102 is effective and safe regardless of the status of *KRAS* and *BRAF*. Furthermore, a significant correlation between QoL and OS was also observed.

Conclusion

The present observational analysis on heavily pretreated elderly patients with mCRC confirms that, in clinical daily practice, TAS-102 achieved a prolongation of OS and PFS[7,8] with a clinical benefit that continued until toxicity or disease progression. TAS-102 was shown to have a manageable safety profile with a favorable impact on toxicity management as determined by on QoL assessment. The effects of population aging and the increased diagnosis of cancer in the elderly will require greater coordination between oncologists and geriatricians to identify which older adults might be able to undergo the various systemic treatments available; for this aim, a complete geriatric assessment is helpful. Furthermore, an analysis of the subgroup of the appeal study [9,11] did not indicate age as a potential factor of increased toxicity or decreased efficacy of TAS-102. Thus, TAS-102 was shown to have a definite clinical activity in a population of patients widely pretreated for mCRC, including those whose disease was refractory to fluorouracil and in all patient subgroups. This study demonstrates how treatment with TAS-102 may represent a valid therapeutic alternative with manageable and relatively contained toxicity in heavily pretreated elderly patients.

Limitations of the study

The limitations of this analysis include the limited number and the nonrandom sampling of patients. However, bearing in mind the retrospective nature of the analysis and the limited number of patients in a single institution, our results yield valid hypotheses for future studies, which should nevertheless be confirmed and validated with prospective randomized trials focused on elderly patients.

Contributions: Data Collection: GC, RD. Data interpretation: GC, RA. Statistical analysis: GC. Manuscript writing: GC, RA. Manuscript editing: all authors. All authors reviewed and approved the final version of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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