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ESMO GASTROINTESTINAL ONCOLOGY

REVIEW

Managing adverse events in patients with metastatic colorectal cancer receiving trifluridine/tipiracil in combination with bevacizumab

M. Fakih[1]*, F. Ciardiello[2], G. W. Prager[3], E. Élez[4], E. Calleja[5], N. Caussé-Amellal[6], J. Taieb[7] & E. Van Cutsem[8]

[1]City of Hope Comprehensive Cancer Center, Duarte, USA; [2]Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples, Italy; [3]Department of Medicine I, Medical University Vienna, Vienna, Austria; [4]Vall d'Hebron Hospital Campus, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]Taiho Oncology, Inc., Princeton, USA; [6]Servier International Research Institute, Suresnes; [7]Hôpital Européen Georges-Pompidou, University Paris-Cité (Paris Descartes), SIRC CARPEM, Paris, France; [8]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

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For patients with metastatic colorectal cancer (mCRC) that is refractory to standard chemotherapy, a recommended standard-of-care treatment in the third-line setting is trifluridine/tipiracil (FTD/TPI) alone or in combination with bevacizumab; other treatment options include fruquintinib or regorafenib. The safety profiles of FTD/TPI and bevacizumab as individual agents are well characterized. Common adverse events (AEs) associated with FTD/TPI include neutropenia, anemia, nausea, and diarrhea, and AEs frequently observed with bevacizumab include hypertension, proteinuria, hemorrhage, venous thromboembolism, and gastrointestinal perforation. Approval of the combination of FTD/TPI plus bevacizumab for the treatment of patients with refractory mCRC in the United States and Europe was based on results from the phase III SUNLIGHT trial. There is clinical value in developing a specific set of recommendations for the prevention or management of the key AEs associated with the combination regimen to inform clinical care and improve patient benefit. In this review, we summarize the safety profile of combination treatment with FTD/TPI plus bevacizumab in patients with refractory mCRC who were enrolled in the SUNLIGHT trial, with a focus on the key AEs of neutropenia, anemia, nausea or vomiting, diarrhea, fatigue, hypertension, and hemorrhage. In addition, we provide recommendations for the management or prevention of these key AEs in clinical practice, based on published literature and expert opinions on effective strategies.

Key words: adverse event, bevacizumab, metastatic colorectal cancer, safety, tipiracil, trifluridine

INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer deaths worldwide.[1] In the United States, the 5-year relative survival among patients with metastatic CRC (mCRC) is 15.7%.[2] With improvements in the efficacy of therapeutic agents, increasing numbers of patients with mCRC are progressing on to third-line (3L) therapy,[3] including fruquintinib, regorafenib, or trifluridine/tipiracil (FTD/TPI) alone or in combination with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab.[3-5]

FTD/TPI is approved in the United States and Europe as a single agent or in combination with bevacizumab for the treatment of adult patients with mCRC who have progressed through, or are not candidates for, anticancer treatment regimens, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, an anti-VEGF biological therapy, and/or (if *RAS* wild-type) an anti-epidermal growth factor receptor therapy.[6,7] In 2015, FTD/TPI monotherapy was approved for the treatment of patients with refractory mCRC, based on results from the double-blind, randomized, phase III RECOURSE trial (NCT01607957) of FTD/TPI versus placebo among patients with mCRC who had progressed after two or more prior regimens.[8]

The primary endpoint of overall survival (OS) was met [median 7.1 versus 5.3 months; hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.58-0.81, $P < 0.001$] and improvement was also seen in the secondary endpoint of progression-free survival (PFS; median 2.0 versus 1.7 months; HR 0.48, 95% CI 0.41-0.57, $P < 0.001$).[8] The most common adverse events (AEs) associated with FTD/TPI in RECOURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%).[8]

In 2023, FTD/TPI in combination with bevacizumab was approved for the 3L treatment of mCRC, based on results from the phase III SUNLIGHT trial, which investigated the

*Correspondence to: Dr Marwan Fakih, City of Hope Comprehensive Cancer Center, 1500 E Duarte Rd, Duarte, CA 91010, USA. Tel: +1-626-256-4673 extension 83087; Fax: +1-626-218-8233
E-mail: mfakih@coh.org (M. Fakih).

combination versus FTD/TPI monotherapy among patients with refractory mCRC.[9] Median OS was significantly longer with FTD/TPI plus bevacizumab versus FTD/TPI monotherapy (10.8 versus 7.5 months; HR 0.61, 95% CI 0.49-0.77, $P < 0.001$) and median PFS was also longer with the combination at 5.6 months versus 2.4 months for FTD/TPI monotherapy (HR 0.44, 95% CI 0.36-0.54, $P < 0.001$).[9] The most common AEs reported for both groups were neutropenia, nausea, and anemia.[9] Based on these results, FTD/TPI plus bevacizumab has become a standard of care for the 3L treatment of patients with refractory mCRC.[3,5]

Bevacizumab is an anti-VEGF monoclonal antibody that is used in the treatment of various different tumor types, including in combination with chemotherapy for the first- and second-line treatment of mCRC.[10,11] Bevacizumab is known to be associated with several key toxicities, including hypertension, proteinuria, hemorrhage, venous thromboembolism, and gastrointestinal perforation.[10-12] Bevacizumab-related AEs have been discussed in previous publications.[12-16] Following the approval of FTD/TPI plus bevacizumab in refractory mCRC, there is an unmet need for the development of specific recommendations for the management of AEs associated with the combination therapy.

The aims of this review are to summarize the safety profile of combination treatment with FTD/TPI plus bevacizumab in patients with refractory mCRC who were enrolled in the SUNLIGHT trial and provide recommendations for the management or prevention of key AEs associated with this regimen in clinical practice, based on published literature and expert opinions on effective strategies.

OVERVIEW OF AES WITH FTD/TPI PLUS BEVACIZUMAB IN THE SUNLIGHT TRIAL

SUNLIGHT (NCT04737187) was a global, open-label, randomized, phase III trial comparing the efficacy and safety of FTD/TPI plus bevacizumab versus FTD/TPI monotherapy in patients with refractory mCRC; full details of the study design and efficacy and safety results have been reported previously.[9] Briefly, patients were randomized 1 : 1 to receive FTD/TPI 35 mg/m^2 orally, twice daily on days 1-5 and 8-12, alone or in combination with bevacizumab 5 mg/kg intravenously on days 1 and 15 of each 28-day cycle.

The primary endpoint was OS, and secondary endpoints included PFS, objective response and disease control rates (per Response Evaluation Criteria in Solid Tumors version 1.1), safety, and quality of life (QoL; assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 and EuroQol 5-Dimension 5-Level questionnaires at baseline and on day 1 of each treatment cycle).[9,17] Assessment of safety included incidence of AEs, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, laboratory tests, physical examinations, vital signs, and the time from randomization to worsening of the Eastern Cooperative Oncology Group performance status (ECOG PS) score from 0/1 to ≥2.[9]

In total, 492 patients were randomly assigned to receive FTD/TPI plus bevacizumab ($n = 246$) or FTD/TPI monotherapy ($n = 246$), and baseline demographic and clinical characteristics were similar between the groups. Median duration of treatment was 2.4-fold longer for patients receiving FTD/TPI plus bevacizumab compared with those receiving FTD/TPI monotherapy (median 5.0 versus 2.1 months, respectively).[9]

The overall incidence of AEs was similar between the two treatment groups (98% in both) and FTD/TPI plus bevacizumab had a safety profile consistent with that of the individual agents, with no additive toxicity (Table 1).[6,9] AEs were manageable and were not associated with deterioration in patients' QoL; both treatment arms showed similar QoL scores from baseline to cycle 6, with no clinically relevant change over time.[17] FTD/TPI plus bevacizumab significantly improved time to worsening of ECOG PS from 0/1 to ≥2 versus FTD/TPI monotherapy (median 9.3 versus 6.3 months, respectively) and prolonged the time to definitive deterioration of QoL scores.[17]

AEs and laboratory abnormalities that were more commonly observed with FTD/TPI plus bevacizumab than with FTD/TPI monotherapy were hypertension (11% versus 2%), nausea (37% versus 27%), and neutrophils decreased (any grade: 80% versus 68%; grade ≥3: 52% versus 39%).[6] There was no increase in the incidence of febrile neutropenia with FTD/TPI plus bevacizumab compared with FTD/TPI monotherapy ($n = 1$ versus $n = 6$, respectively).[9] Commonly observed AEs across both treatment arms of

Table 1. Most common AEs reported in the SUNLIGHT trial (≥10% of patients)[6]

Event (any cause)	FTD/TPI plus bevacizumab ($N = 246$)		FTD/TPI monotherapy ($N = 246$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematological laboratory abnormality, %				
Neutrophils decreased	80	52	68	39
Hemoglobin decreased	68	5	73	11
Platelets decreased	54	4	29	<1
Gastrointestinal AE, %				
Nausea	37	2	27	2
Diarrhea[a]	21	1	19	2
Abdominal pain[a]	20	3	18	4
Decreased appetite	20	1	15	1
Vomiting[a]	19	1	15	2
Stomatitis[a]	13	<1	4	0
Constipation	11	0	11	1
General/other AE, %				
Fatigue[a]	45	5	37	8
Musculoskeletal pain[a]	18	1	11	2
Hypertension[a]	11	6	2	1
Hemorrhage[a]	10	1	4	1

AE, adverse event; FTD/TPI, trifluridine and tipiracil.
[a]Represents a composite of multiple related terms.

the SUNLIGHT trial were consistent with those observed in other clinical studies of FTD/TPI therapy (i.e. neutropenia, anemia, nausea, and diarrhea).[18]

The fluoropyrimidines 5-fluorouracil and capecitabine are the backbone of many chemotherapy regimens in mCRC[4]; however, cardiotoxicity is an AE of concern (1%-35% incidence) with these agents.[19,20] Therefore, it is notable that FTD/TPI is considered a cardio-gentle agent,[21] which is corroborated by the observation that there were no observed incidences of cardiotoxicity with FTD/TPI in the SUNLIGHT trial.[9]

For patients with mCRC harboring dihydropyrimidine dehydrogenase (DPD) deficiency, fluoropyrimidines are associated with severe toxicity. In contrast, the pharmacokinetic pathway of trifluridine is independent of DPD, rendering FTD/TPI suitable for use at the standard dose in this patient population.[22]

OVERVIEW OF AES WITH FTD/TPI IN THE RECOURSE TRIAL

In the RECOURSE trial, 800 patients were randomly assigned to receive FTD/TPI ($n = 534$) or placebo ($n = 266$).[8] The overall incidence of AEs of any grade was similar between the two treatment groups (98% for FTD/TPI and 93% for placebo) but the incidence of grade $\geq$3 AEs was higher for FTD/TPI (69%) than placebo (52%).[8] The most common AEs in the FTD/TPI arm were anemia (77%), leukopenia (77%), and neutropenia (67%).[8] The incidence of grade $\geq$3 anemia (18% versus 3%) and thrombocytopenia (5% versus $<$1%) was higher in the FTD/TPI group than in the placebo group.[8] Gastrointestinal AEs of grade $\geq$3 nausea (2% versus 1%), vomiting (2% versus $<$1%), and diarrhea (3% versus $<$1%) were also higher in the FTD/TPI group than in the placebo group.[8] In addition, the most common clinically significant grade $\geq$3 AEs associated with FTD/TPI were neutropenia (38%) and leukopenia (21%); 4% of patients had febrile neutropenia.[8] The incidence of fatigue was higher in the FTD/TPI group than in the placebo group (35% versus 23%).[8] Overall, the safety findings for the FTD/TPI group in RECOURSE were generally comparable with findings from the SUNLIGHT trial, particularly for the monotherapy arm. Hypertension was not a commonly reported AE in the RECOURSE trial as it was for the FTD/TPI plus bevacizumab combination arm in the SUNLIGHT trial[9]; this is not unexpected, as hypertension is a known AE with bevacizumab use. Thus, the strategy for management of the key AEs presented below is applicable for patients receiving either FTD/TPI monotherapy or in combination with bevacizumab.

MANAGEMENT OF KEY AES ASSOCIATED WITH FTD/TPI PLUS BEVACIZUMAB

Effective management strategies can mitigate the impact of AEs, extending treatment duration and benefits. The safety profiles of FTD/TPI and bevacizumab as individual treatments are well characterized.[6,7,10,11] A better understanding of AEs associated with the combination of FTD/TPI plus bevacizumab in patients with mCRC is needed to guide clinical care and improve patient outcomes.

The recommended dose of FTD/TPI is 35 mg/m^2/dose administered orally twice daily with food on days 1 through 5 and days 8 through 12 of each 28-day cycle.[6,7] When FTD/TPI is used in combination with bevacizumab for the treatment of mCRC, the recommended dose of bevacizumab is 5 mg/kg of body weight given intravenously once every 2 weeks of each 28-day cycle.[7,10,11] For patients with severe renal impairment (creatinine clearance of 15-29 ml/min as determined by the Cockcroft–Gault formula), the dose should be reduced to 20 mg/m^2 twice daily, with a further reduction to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily. No dose escalations are permitted after dose reductions.[6,7] Guidance for the management of AEs associated with FTD/TPI include dose modifications until AE resolution, enabling the patient to continue treatment and prolong benefits; however, dose reductions are not recommended for bevacizumab (Table 2).[6,7,10,11]

In SUNLIGHT, AEs that were attributed to FTD/TPI were observed in 89.8% and 81.3% of patients in the FTD/TPI plus bevacizumab and FTD/TPI monotherapy arms, respectively, and bevacizumab-related AEs were reported in 48.4% of patients in the combination group. There were no treatment-related deaths.[9] Dose delays and reductions enabled patients to remain on FTD/TPI treatment while minimizing observed AEs. Dose reductions were reported in 16.3% and 12.2% of patients in the FTD/TPI plus bevacizumab combination and FTD/TPI monotherapy arms, respectively; dose delays were reported in 69.5% and 53.3%, respectively.[9] In both arms, 12.6% of patients had AEs of any cause that led to discontinuation of the study treatment; 2.4% and 2.0% of these AEs in the combination and monotherapy arms, respectively, were determined by investigators to be treatment related.[9]

The following sections provide further detail on the key treatment-emergent AEs observed with FTD/TPI plus bevacizumab in SUNLIGHT, along with recommendations for their management in clinical practice (Table 3).

HEMATOLOGIC AES

Neutropenia

In SUNLIGHT, decreased neutrophil counts of any grade were observed in 80% (grade $\geq$3: 52%) and 68% (grade $\geq$3: 39%) of patients in the FTD/TPI plus bevacizumab and FTD/TPI monotherapy arms, respectively (Table 1).[6] The frequency of concomitant granulocyte colony-stimulating factor (G-CSF) administration during the treatment period was 29.3% with FTD/TPI plus bevacizumab and 19.5% with FTD/TPI monotherapy.[9]

Results from a *post hoc* analysis of SUNLIGHT indicated that patients who had grade $\geq$3 neutropenia or decreased neutrophil count had better efficacy outcomes compared with those who had grade $<$3 or no incidence, and this was observed in both treatment arms.[31] In the FTD/TPI plus bevacizumab arm, grade $\geq$3 neutropenia or decreased neutrophil count was associated with prolonged median OS (HR 0.37, 95% CI 0.26-0.52, $P < 0.0001$) and median PFS

Table 2. Guidance on dose modifications for key AEs with FTD/TPI and bevacizumab[6,7,10,11]

FTD/TPI	
Do not initiate the cycle of FTD/TPI until:	• ANC $\geq 1.5 \times 10^9$/l • Febrile neutropenia is resolved • Platelets $\geq 75 \times 10^9$/l • Grade 3/4 nonhematological AEs are resolved to grade 1 or baseline
Within a treatment cycle, withhold FTD/TPI for any of the following:	• ANC $<0.5 \times 10^9$/l • Febrile neutropenia • Platelets $<50 \times 10^9$/l • Grade 3 or 4 nonhematological AEs
After recovery, resume FTD/TPI after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur (maximum three dose reductions permitted; do not escalate FTD/TPI dosage after it has been reduced):	• Febrile neutropenia • Uncomplicated grade 4 neutropenia (ANC 0.5 $\times 10^9$/l that has recovered to ANC $\geq 1.5 \times 10^9$/l) or thrombocytopenia (platelets $<25 \times 10^9$/l that has recovered to platelets $\geq 75 \times 10^9$/l) that results in >1 week's delay in start of next cycle • Nonhematological grade 3 or 4 AEs except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or grade 3 diarrhea responsive to anti-diarrheal medication
Permanently discontinue FTD/TPI in:	• Patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily
A maximum of three dose reductions are permitted (to a minimum dose of 20 mg/m^2/dose twice daily or 15 mg/m^2/dose twice daily in severe renal impairment)	
Do not increase the dose after it has been reduced	

Bevacizumab		
Key AE	**Severity**	**Dose modification**
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue bevacizumab
	• Severe (grade 3/4) hypertension	Withhold bevacizumab if not controlled with medical management; resume once controlled
	Additional guidance: • Monitor BP every 2-3 weeks during treatment with bevacizumab • Treat with appropriate antihypertensive therapy and monitor BP regularly • Continue to monitor BP at regular intervals in patients with bevacizumab-induced or -exacerbated hypertension after discontinuing bevacizumab	
Hemorrhage	• Grade 3/4 • Recent history of pulmonary hemorrhage or hemoptysis of $\geq$1/2 tsp (>2.5 ml red blood)	Discontinue bevacizumab Withhold bevacizumab
	• Intracranial bleeding	Discontinue bevacizumab
	Additional guidance: • Patients should be monitored for signs and symptoms of CNS bleeding	
GI perforations and fistulae	• Any-grade GI perforation • Any-grade tracheoesophageal fistula • Grade 4 fistula • Fistula formation involving any internal organ	Discontinue bevacizumab

AE, adverse event; ANC, absolute neutrophil count; BP, blood pressure; CNS, central nervous system; FTD/TPI, trifluridine and tipiracil; GI, gastrointestinal.

Table 3. Recommendations for the management of key AEs associated with FTD/TPI plus bevacizumab[a]

AE	Recommendations for monitoring, supportive care, and management
Hematological	
Neutropenia and febrile neutropenia[23-26]	• Monitoring of blood counts • Assessment of patient risk factors for febrile neutropenia • Prophylactic or therapeutic G-CSF administration
Anemia[23,25-28]	• Monitoring of blood counts and iron levels/saturation • RBC transfusion • Iron supplementation in the event of iron deficiency • ESAs (generally to be limited to the treatment of patients receiving chemotherapy with palliative intent and who are expected to have short survival)
Gastrointestinal	
Nausea and vomiting[26]	• Antiemetic therapy, such as domperidone or metoclopramide and/or alizapride and/or 5-HT$_3$ antagonists (e.g. oral dolasetron 100 mg/day, oral ondansetron 16-24 mg/day, oral granisetron 1-2 mg/day, or granisetron 3.1 mg/day via transdermal patch) • Adjunct therapy with a proton pump inhibitor and/or a benzodiazepine (e.g. lorazepam 0.5-2 mg every 6 h as needed during days 1-4 of each cycle) or olanzapine ◦ For breakthrough emesis, an antiemetic from a different class should be used: benzodiazepine (e.g. lorazepam or alprazolam), cannabinoid (e.g. dronabinol or nabilone), corticosteroid (e.g. dexamethasone), phenothiazine (e.g. prochlorperazine or promethazine), or atypical antipsychotic (e.g. olanzapine)
Diarrhea[26,29]	• Dietary interventions • Dietary modifications • Antidiarrheal medication (e.g. oral loperamide hydrochloride 2-4 mg $\pm$ oral diphenoxylate/atropine 2.5/0.025 mg for grade 1/2 diarrhea, or octreotide acetate for persistent grade 3/4 diarrhea) • IV fluids • Antibiotics in the case of specific infections
General/other	
Fatigue[26]	• Regular screening • Patient self-monitoring • Dietary adjustments
Hypertension[12,30]	• Assessment of cardiovascular risk • Monitoring of BP before bevacizumab infusions and at home • Antihypertensive therapy • ACE inhibitors • ARBs • Beta blockers • Calcium channel blockers
Hemorrhage[12]	• Evaluate potential risk factors (e.g. gastric ulcers, brain tumors) • MRI of the brain (if baseline brain tumor is present)

ACE, angiotensin-converting enzyme; AE, adverse event; ARB, angiotensin II receptor blocker; BP, blood pressure; ESA, erythropoiesis-stimulating agent; FTD/TPI, trifluridine and tipiracil; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; MRI, magnetic resonance imaging; RBC, red blood cell.

[a]These recommendations have been developed as guidance for AE management; they are not included in the prescribing information for either FTD/TPI or bevacizumab.

(HR 0.41, 95% CI 0.31-0.55, $P < 0.0001$); in the FTD/TPI monotherapy arm, median OS (HR 0.45, 95% CI 0.32-0.63, $P < 0.0001$) and median PFS (HR 0.48, 95% CI 0.35-0.64, $P < 0.0001$) were also prolonged among patients with grade $\geq$3 neutropenia or decreased neutrophil count.[31]

In clinical practice, hematological AEs such as neutropenia should be observed by the monitoring of blood counts (Table 3). Complete blood cell counts should be obtained before the initiation of FTD/TPI and on day 15 of each cycle.[6] A decreased neutrophil count is defined as an absolute neutrophil count (ANC) of less than the lower limit of normal (<LLN) per mm^3 of blood; grade $\geq$3 decreased neutrophil count is defined as an ANC <1000/mm^3; and febrile neutropenia is characterized by an ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of $\geq$38°C (100.4°F) for >1 h.[32]

Prophylactic administration of G-CSF (filgrastim, pegfilgrastim, or biosimilars) is recommended for the management of chemotherapy-induced neutropenia, to return the ANC to normal levels, and for the prevention of febrile neutropenia in patients receiving treatment with myelosuppressive chemotherapy agents.[23-26] The authors suggest that patients who receive prophylactic G-CSF with second-line regimens can also receive it when given FTD/TPI in the 3L setting; however, the use of G-CSF prophylaxis is not mentioned in the prescribing information for FTD/TPI monotherapy or in combination with bevacizumab. Secondary prophylaxis with G-CSF has been shown to be associated with maintenance of FTD/TPI dose intensity.[33] In the nonrandomized LONGBOARD prospective cohort trial (NCT04166604), among patients with mCRC treated with FTD/TPI monotherapy and who received secondary prophylaxis for grade $\geq$3 neutropenia, 91.9% (95% CI 83.2% to 97.0%) were free from dose reduction or cycle postponement for >7 days at 6 months.[33]

Therapeutic use of the short-acting G-CSF filgrastim (or biosimilar) is recommended for patients who develop febrile neutropenia despite prior preventive short-acting G-CSF administration, but filgrastim is not recommended for those who have received prior preventive long-acting G-CSF (pegfilgrastim or biosimilar).[23,25] Initiation of G-CSF should be considered in patients who present with risk factors for infection-associated complications or poor clinical outcomes and who have received no prior prophylactic G-CSF.[23,25,26]

Anemia

Decreased hemoglobin of any grade was observed in 68% (grade $\geq$3: 5%) of patients in SUNLIGHT who received the combination therapy and in 73% (grade $\geq$3: 11%) of those who received FTD/TPI monotherapy (Table 1).[6] Of note, the incidence of anemia (both any grade and grade $\geq$3) was lower in the FTD/TPI plus bevacizumab combination arm than in the FTD/TPI monotherapy arm. This is consistent with what has been observed by the authors in clinical practice.

As with neutropenia, the development of anemia should be observed by the monitoring of blood counts and iron levels or iron saturation (Table 3). Anemia is defined by a hemoglobin level <LLN g/dl of blood and grade $\geq$3 anemia is characterized by a hemoglobin level <8.0 g/dl.[32] In clinical practice, recommendations for the management of symptomatic anemia include red blood cell transfusions, iron supplementation in the event of iron deficiency, or erythropoiesis-stimulating agents (ESAs).[23,25-27] Clinicians are often hesitant to use ESAs due to the United States Food and Drug Administration black box warning and possible detrimental effects. Some clinicians recommend that ESA use should be limited to the treatment of patients who require frequent repeat transfusions. Additionally, due to the potential for ESA to stimulate tumor growth, updated guidelines from the American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) suggest that ESA use for treating anemia in patients with cancer should be limited to those receiving chemotherapy with palliative intent and who are expected to have short survival.[28] Transfusions are generally considered for high-risk patients who are asymptomatic for anemia and who have comorbidities, such as chronic pulmonary disease or coronary artery disease.[26]

GASTROINTESTINAL AES

Nausea and vomiting

Any-grade nausea and vomiting, respectively, were observed in 37% and 19% (grade $\geq$3: 2% and 1%) of patients in SUNLIGHT who received the combination therapy and in 27% and 15% (grade $\geq$3: 2% and 2%) of those who received FTD/TPI monotherapy (Table 1).[6]

In clinical practice, administering antiemetic therapy can help to prevent the onset of nausea and vomiting (Table 3).[26] FTD/TPI therapy is considered to have a moderate-to-high emetogenic risk, for which the recommended therapy is a prophylactic 5-hydroxytriptamine 3 antagonist such as ondansetron, dolasetron, or granisetron.[26] Adjunct therapy with a benzodiazepine (such as lorazepam), a proton pump inhibitor, or olanzapine may also be used. An antiemetic from a different class should be used for the treatment of breakthrough emesis (benzodiazepine, cannabinoid, corticosteroid, phenothiazine, or atypical antipsychotic).[26] Dietary interventions may also be recommended for managing nausea; these could include reduced portion sizes, increased frequency of meals, avoiding the skipping of meals, reducing the intake of liquids during meals, and eating foods at room temperature.[26]

Diarrhea

Diarrhea of any grade was observed in 21% and 19% (grade $\geq$3: 1% and 2%) of patients in the FTD/TPI plus bevacizumab and FTD/TPI monotherapy arms of SUNLIGHT, respectively (Table 1).[6]

The recommendation for the initial management of grade 1/2 diarrhea in clinical practice is dietary modification (Table 3), such as more frequent meals with reduced portion sizes and the elimination of alcohol, lactose, and

high-osmolar supplements from the diet.[26,29] Treatment with loperamide hydrochloride (an oral opiate) alone or in combination with diphenoxylate/atropine is also recommended for grade 1/2 diarrhea. For grade 3/4 diarrhea and severe dehydration, octreotide acetate (a somatostatin analog) may be administered subcutaneously or intravenously. Other recommendations for managing diarrhea include administering intravenous fluids, or antibiotics in the case of specific infections.[26,29]

GENERAL/OTHER AES

Fatigue

Any-grade fatigue was reported in 45% (grade ≥3: 5%) of patients in the FTD/TPI plus bevacizumab arm and 37% (grade ≥3: 8%) of patients in the FTD/TPI monotherapy arm of SUNLIGHT (Table 1).[6]

Fatigue is a multifactorial symptom that may result from the disease, the treatment regimen, emotional distress, nutritional problems, sleep disturbance, or other comorbidities[26]; in addition, fatigue is the most common symptom associated with chemotherapy-induced anemia.[34] In clinical practice, all patients with mCRC should be regularly screened for fatigue throughout the treatment journey and encouraged to utilize general strategies for its management (Table 3); for example, these may include dietary changes, physical activity, psychosocial interventions, or massage therapy.[26]

Hypertension

Hypertension of any grade was reported in 11% (grade ≥3: 6%) of patients in the FTD/TPI plus bevacizumab arm of SUNLIGHT and 2% (grade ≥3: 1%) of those in the FTD/TPI monotherapy arm (Table 1).[6]

In clinical practice, it is standard for patients to have their cardiovascular risk assessed and blood pressure (BP) checked before starting bevacizumab therapy and before initiation of each infusion (Table 3).[12,30] Assessment of cardiovascular risk includes the evaluation of various risk factors, including underlying cardiovascular disease, chronic kidney disease, diabetes mellitus, hyperlipidemia, obesity, tobacco use, family history of hypertension, and advanced age.[12]

United States and European guidelines for managing hypertension are aimed at the general patient population and are not specific to patients with cancer or those receiving bevacizumab.[30] One set of expert guidance for managing hypertension in patients with ovarian and cervical cancer receiving bevacizumab recommends the initiation of treatment in patients with a clinic BP <160/100 mmHg[30]; for those with a clinic BP ≥160/100 mmHg, ambulatory or home BP monitoring is recommended to identify sustained hypertension. If the average BP is ≥150/95 mmHg over ≥4 consecutive days, bevacizumab initiation should be delayed and antihypertensive therapy started.[30] However, definitions of hypertension vary across regions. The American College of Cardiology/American Heart Association criteria definition of hypertension is BP ≥130/80 mmHg and that of the European Society of Hypertension is BP ≥140/90 mmHg.[35] Similarly, for patients with refractory mCRC receiving FTD/TPI plus bevacizumab, clinicians recommend initiating antihypertensive treatment in patients with BP >140/90 mmHg.

In antihypertensive therapy-naïve patients who have no significant pre-existing cardiovascular disease, antihypertensive therapy may be started with amlodipine 5 mg daily and patients should be reassessed after ≥2 weeks, after which point bevacizumab can be initiated if the average ambulatory or home BP is <150/95 mmHg. If BP remains ≥150/95 mmHg, an angiotensin-converting enzyme (ACE) inhibitor (e.g. perindopril 2 mg daily) or an angiotensin II receptor blocker (e.g. losartan 50 mg daily) may be added. If BP remains ≥150/95 mmHg after this, indapamide 2.5 mg daily may be added. If this is unsuccessful, the dose of ≥1 antihypertensive therapy may be increased and/or low-dose spironolactone may be added (if normal renal function and serum potassium is <4.5 mmol/l) and/or the patient may be referred to a hypertension specialist.[30]

After initiating bevacizumab, the threshold for continued therapy is a BP <160/100 mmHg and patients should be encouraged to continue home BP monitoring twice daily.[12,30] Bevacizumab-related hypertension can be treated using ACE inhibitors, calcium channel blockers, beta blockers, or diuretics.[12] If a patient has a hypertensive crisis or hypertension cannot be adequately controlled using antihypertensives or if there are signs of hypertensive encephalopathy, bevacizumab should be permanently discontinued.[12]

Hemorrhage

In SUNLIGHT, any-grade hemorrhage was reported in 10% (grade ≥3: 1%) and 4% (grade ≥3: 1%) of patients in the FTD/TPI plus bevacizumab and FTD/TPI monotherapy arms, respectively (Table 1).[6]

Hemorrhage, most commonly epistaxis, is a frequently reported bevacizumab-related AE.[12] Hemorrhage can occur at various anatomic locations and is defined as an acute loss of blood from a damaged blood vessel. The severity of hemorrhage is characterized by the percentage loss of blood volume.[36] In healthy adults, the average volume of blood circulating at any given time is 4.5-5.5 l or 70-90 ml/kg. A hemorrhage is categorized as class I, II, III, or IV when the total loss of blood volume is ≤15%, 15%-30%, 30%-40%, or >40%, respectively.[36]

To minimize the risk of hemorrhage, patients should be assessed for potential risk factors before bevacizumab initiation, including assessment of the disease site for any signs of bleeding (Table 3).[12] Common risk factors include gastric ulcers, which can lead to gastrointestinal hemorrhage, and baseline brain tumors, which can lead to intracranial bleeding. For the latter, magnetic resonance imaging of the brain is recommended to differentiate between active bleeding and nonactive prior hemorrhages.[12]

CONCLUSIONS

Results from the phase III SUNLIGHT trial demonstrated that the safety profile of FTD/TPI plus bevacizumab was

consistent with the individual safety profiles of FTD/TPI monotherapy and bevacizumab, and there were no clinically relevant changes over time in patient-reported QoL scores between the two treatment arms. The most common AEs reported in both groups were neutropenia, nausea, and anemia. Hypertension, nausea, and neutropenia were more common with FTD/TPI in combination with bevacizumab than with FTD/TPI monotherapy. Most AEs were grade 1 or 2, with the exception of neutropenia and hypertension, neither of which were associated with symptomatology and were effectively managed with growth factors and antihypertensive medications, respectively.

Key AEs anticipated with FTD/TPI plus bevacizumab in clinical practice include neutropenia, anemia, nausea and vomiting, diarrhea, fatigue, hypertension, and hemorrhage. With the exception of neutropenia, key treatment-emergent AEs leading to FTD/TPI or bevacizumab dose modifications were infrequent in SUNLIGHT and most patients were able to continue at the standard dose of both agents.

Enhancing the understanding of AEs associated with FTD/TPI in combination with bevacizumab for the treatment of patients with mCRC may further improve clinical care and outcomes. Management of AEs associated with the individual agents can be considered to guide the effective management of AEs associated with combination treatment.

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