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Adherence, Dosing, and Managing Toxicities With Trifluridine/Tipiracil (TAS-102)

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Abstract

Trifluridine/tipiracil (TAS-102) is a new oral combination therapy approved by the US Food and Drug Administration for the treatment of patients with metastatic colorectal cancer who are refractory to or intolerant of standard chemotherapy. This agent consists of a thymidine-based nucleoside analog (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil), which is included to reduce the degradative breakdown of trifluridine. In the phase 3 RECURSE trial, trifluridine/tipiracil showed significant improvement in overall survival when compared with placebo. Trifluridine/tipiracil is administered at 35 mg/m²/dose orally twice daily in a 28-day cycle consisting of 5 treatment days/2 rest days for 2 weeks followed by a rest period of 2 weeks. Because trifluridine/tipiracil is a completely oral chemotherapy regimen, patient adherence to treatment is an important consideration. It is also critical to have strategies in place for managing toxicities, as side effects may have a negative impact on patient adherence. The most frequent adverse events reported in patients with metastatic colorectal cancer receiving trifluridine/tipiracil in the phase 3 RECURSE trial were myelosuppression, nausea/vomiting, diarrhea, decreased appetite, and fatigue. This review aims to provide clinicians with practical recommendations for facilitating patient adherence to oral chemotherapy, managing trifluridine/tipiracil dosing, and addressing the most common adverse events in patients receiving trifluridine/tipiracil therapy.

Keywords

fluoropyrimidine; metastatic colorectal cancer; nucleoside analog; oral chemotherapy; patient adherence; RECURSE trial

Introduction

An estimated 134,490 Americans will be diagnosed with colorectal cancer (CRC) in 2016, and nearly 50,000 will die from this disease.¹ CRC is the third most common cancer

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diagnosis for both men and women in the United States and the second most common cause of cancer death for both sexes.¹ Despite a steady decline in CRC-associated mortality over the past 2 decades, the 5-year survival rate for patients diagnosed with advanced, metastatic disease remains low (8% to 12%).¹ There is clearly a significant need for well-tolerated, effective treatment options for patients with metastatic CRC (mCRC) who are refractory to standard chemotherapy. Treatment options for patients with mCRC who progress beyond first- and second-line therapy remain limited, and they are determined by the previous treatment regimens received by the patient.²

Regorafenib is a small-molecule multikinase inhibitor, which is currently approved for the treatment of patients with mCRC in the third-line or later setting.² The CORRECT trial was a randomized phase 3 study comparing regorafenib with placebo in patients with mCRC who had received all standard therapies (N=760); this study showed significant improvement in median overall survival (OS) in the regorafenib arm when compared with the placebo arm (6.4 vs 5.0 months; hazard ratio [HR], 0.77; 95% CI, 0.64–0.94; 1-sided $P=.0052$).³ Treatment-related adverse events (AEs) were observed in 465 patients (93%) in the regorafenib arm and in 154 patients (61%) in the placebo arm. The most common Grade 3 AEs in patients receiving regorafenib were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), and skin rash (6%). These AEs may necessitate dose modifications and/or permanent discontinuation of the drug.⁴

Trifluridine/Tipiracil (TAS-102)

Trifluridine/tipiracil (TAS-102) is a new oral fluoropyrimidine therapy approved by the national health authorities in the United States, Europe, and Japan for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor biologic product, and an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, if *RAS* wild-type. Trifluridine is a thymidine-based nucleoside analog that is metabolized to the triphosphate metabolite, which is then incorporated into DNA, resulting in inhibition of DNA synthesis and function. The trifluridine monophosphate inhibits thymidylate synthase (TS), which is the key enzyme that provides for the sole intracellular source of thymidylate, an essential nucleotide precursor for DNA biosynthesis. In contrast to the 5-fluorouracil (5-FU) metabolite fluorodeoxyuridine monophosphate (FdUMP), trifluridine monophosphate has been shown to be a much weaker inhibitor of TS, and it is believed that TS inhibition does not play a major role in the biological activity of the molecule. Tipiracil is a thymidine phosphorylase (TP) inhibitor, which inhibits trifluridine degradative metabolism by TP; this inhibition leads to enhanced activation of trifluridine to the monophosphate and triphosphate cytotoxic metabolites.^{5,6} The mechanism of action of trifluridine/tipiracil is, therefore, somewhat different from that of 5-FU, a fluoropyrimidine base analog that has been the foundation of mCRC treatment for approximately the last 50 years.^{7,8} The main cytotoxic effect of 5-FU is primarily mediated through inhibition of TS, which leads to inhibition of DNA synthesis (Figure 1).^{7,8} In addition, 5-FU also exerts its biological activity through incorporation of the 5-FU metabolite fluorodeoxyuridine triphosphate (FdUTP) into DNA, leading to inhibition of DNA synthesis and function, and through incorporation of the 5-FU

metabolite fluorouridine triphosphate (FUTP) into RNA, resulting in inhibition of RNA synthesis and function.⁷

The clinical efficacy and safety of trifluridine/tipiracil in patients with mCRC refractory or intolerant to standard therapies were evaluated in the international, randomized phase 3 RECURSE trial (N=800).⁹ The enrollment criteria for RECURSE included 2 prior lines of standard chemotherapy, which included prior fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab.⁹ Patients with *KRAS* wild-type tumors were also required to have previously received an anti-EGFR antibody (either cetuximab or panitumumab).⁹ Treatment with trifluridine/tipiracil resulted in significantly improved OS when compared with placebo (median OS, 7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58–0.81; $P<.001$).⁹ Significant improvements were observed in the secondary endpoints of progression-free survival (PFS; 2.0 vs 1.7 months; HR, 0.48; 95% CI, 0.41–0.57; $P<.001$) and disease control rate (the percentage of patients with complete response, partial response, or stable disease; 44% vs 16%; $P<.001$) with trifluridine/tipiracil versus placebo.⁹ Patients receiving trifluridine/tipiracil also experienced a much longer time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status than those in the placebo group (median time for change of ECOG performance status from a baseline of 0 or 1 to 2, 5.7 vs 4.0 months; HR, 0.66; 95% CI, 0.56–0.78; $P<.001$).⁹ Of note, despite the improvements in OS and PFS, the objective response rate (complete response or partial response) was low at only 1.6% with trifluridine/tipiracil compared with 0.4% in the placebo arm ($P=.29$).

With respect to safety profile, treatment with the trifluridine/tipiracil group (N=533) was associated with a higher frequency of Grade 3 AEs when compared with the placebo group (69% vs 52%).⁹ The incidence of Grade 3 neutropenia was 38% in patients treated with trifluridine/tipiracil, but there was a relatively low incidence of febrile neutropenia (4%). In comparison, no cases of Grade 3 neutropenia were observed in the placebo group.⁹ There was one treatment-related death due to septic shock.⁹ The trifluridine/tipiracil group had a higher incidence of Grade 3 anemia (18% vs 3%) and Grade 3 thrombocytopenia (5% vs <1%) compared with the placebo group and higher rates of Grade 3 nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%).⁹ There were no clinically meaningful differences between the treatment groups in the percentage of patients with Grade 3 hepatic or renal laboratory abnormalities, decreased appetite, stomatitis, hand-foot syndrome, or cardiac ischemia.⁹

Trifluridine/tipiracil dosing

The recommended dosing regimen of trifluridine/tipiracil is 35 mg/m²/dose orally twice daily on days 1 through 5 and days 8 through 12 of each 28-day cycle.¹⁰ Each treatment cycle is followed by a 2-week rest period, the goal of which is to allow for blood counts to recover before the next treatment cycle is administered. In the case of a missed dose, patients are advised to take the next dose as scheduled without attempting to make up for the missed dose.¹⁰

In general, no dose adjustments are recommended for patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN; or TB < ULN × 1–1.5 and any AST). Patients with

moderate ($TB < ULN \times 1.5-3$ and any AST) or severe hepatic impairment ($TB > ULN \times 3$ and any AST) were not enrolled in the RECOURSE trial,¹⁰ so caution is required when using trifluridine/tipiracil in the setting of moderate to severe hepatic dysfunction. In Europe, administration of the drug is not recommended in patients with moderate or severe hepatic dysfunction.¹¹ With respect to renal dysfunction, no dose adjustments are recommended for patients with mild renal impairment (creatinine clearance [CrCL] of 60–89 mL/min) (Table 1). Patients with moderate renal impairment (CrCL of 30–59 mL/min) may experience an increased risk of toxicity, which would then require dose modifications.¹⁰ Patients with severe renal impairment (CrCL <30 mL/min) were not enrolled in the RECOURSE trial, and caution is recommended when using trifluridine/tipiracil in this cohort of patients.¹⁰ In Europe, administration is not recommended for this group of patients.¹¹ At the present time, organ dysfunction studies are ongoing in the US to determine how best to dose trifluridine/tipiracil in patients with hepatic and/or renal dysfunction.

Association Between Onset of Neutropenia and Survival

The potential predictive value of neutropenia caused by cytotoxic drugs has been reported in several cancer types.^{12–15} A post-hoc analysis of RECOURSE was performed to determine the potential correlation between onset of Grade 3 neutropenia and clinical benefit.¹⁶ Of 533 patients who received trifluridine/tipiracil, 75 (14%) developed Grade 3 neutropenia in treatment cycle 1, 86 (16%) in cycle 2, and 39 (7%) in cycle 3.¹⁶ Onset of Grade 3 neutropenia during any cycle was associated with longer median OS and PFS compared with no onset of neutropenia.¹⁶

This association between the occurrence of neutropenia after trifluridine/tipiracil and survival benefit has been reported by other investigators.^{17,18} The RECOURSE data indicated that such survival benefit occurred regardless of whether the initial onset of neutropenia occurred after cycle 1, cycle 2, or with later cycles of therapy. However, this observation does not support that grade 3 neutropenia could be aimed or tolerated to improve survival while on TAS-102 therapy. In general, neutropenia is a manageable treatment-related toxicity. Clinicians should use caution when considering dose reductions of trifluridine/tipiracil in patients who present with mild neutropenia. In this situation, it may be prudent to delay treatment, as dose reductions may negatively affect the clinical efficacy of the drug whereas a dose delay may not have the same negative consequence. It should also be noted that, as was observed in the RECOURSE study, Grade 3 neutropenia may occur for the first time after cycle 1.

Oral Chemotherapy: Adherence and Other Considerations

Trifluridine/tipiracil is a completely oral chemotherapy regimen. There is now a growing body of evidence showing that the large majority of patients prefer oral chemotherapy, citing convenience, problems with intravenous access or needles, and a better chemotherapy-taking environment as their main reasons.^{19–22} However, despite this preference for oral chemotherapy, patients are clearly not willing to compromise clinical benefit in terms of lower response rate or shorter duration of response. Moreover, patients and their caregivers may not be sufficiently prepared to play a more active role in their chemotherapy by taking

greater responsibility for managing dosing schedules, toxicities, and other considerations associated with an oral regimen.¹⁹ Patients may also have the misperception that, compared with parenteral chemotherapy, oral chemotherapy is safer and associated with fewer toxicities.¹⁹

Adherence to oral chemotherapy

It is important to consider adherence when assessing whether a patient is a potential candidate for oral chemotherapy.¹⁹ Studies evaluating adherence to oral chemotherapy in adults have shown variable results, with rates of adherence and persistence ranging from <20% to 100%.^{23,24} Several factors may influence patient adherence, with perhaps the most important one being management of the symptoms and/or side effects of therapy.^{23,25}

One potential advantage to trifluridine/tipiracil therapy is the relatively low number of drug-drug interactions; this results from the fact that neither trifluridine nor tipiracil is metabolized by the liver P450 enzymes.¹⁰ However, the rate and extent of absorption of trifluridine/tipiracil are reduced by food, and the recommendation is for this agent to be taken within 1 hour after a meal.¹⁰ A pharmacokinetic study evaluating food effects in patients with solid tumors (N=16) found that the maximum concentration ($C_{\max}$) of trifluridine was decreased by approximately 40% when trifluridine/tipiracil was administered after a high-fat, high-calorie meal (110 kcal of protein, 180 kcal of carbohydrates, and 360–430 kcal of fat) with no associated change in systemic drug exposure (area under the curve of trifluridine).²⁶ This decrease in $C_{\max}$ of trifluridine was believed to be beneficial in reducing the risk of myelosuppression, since a significant correlation between $C_{\max}$ of trifluridine and decreased neutrophil count was observed.²⁶ Patients receiving trifluridine/tipiracil should be encouraged to speak with physicians, nurses, and/or dietitians/nutritionists for counseling on nutrition and managing eating problems.²⁷ However, based on the clinical data generated thus far, it appears that patients do not need to be concerned about the particular type of food content or diet as they do not have a critical impact on absorption and bioavailability. Furthermore, it is especially critical for patients and their caregivers to be educated on when to take trifluridine/tipiracil, with the recommendation being that the drug should be taken within 1 hour after completion of morning and evening meals.

Patient and caregiver education

One of the potential downsides with oral chemotherapy is that there are fewer required visits to the clinic than with intravenous chemotherapy, which then provides a reduced number of opportunities for patient education, counseling, and communication.^{19,25} Therefore, communication with the patient prior to the initiation of oral chemotherapy is viewed as a critical issue in maintaining patient adherence. Oncologists, mid-level providers, and nurses should engage in a thoughtful discussion with patients and caregivers about the patient's commitment to adherence. They must also discuss the possibility of any socioeconomic, psychosocial, financial, or other barriers that may prevent the patient from obtaining or taking the drug as prescribed.^{19,25} An important financial issue relates to the oral chemotherapy parity law, which states that oral chemotherapy should be covered to the same extent as intravenous chemotherapy. While there is a federal law that mandates equal

coverage for oral chemotherapy, it is currently up to the individual state legislatures to ensure that this law is enforced. To date, 6 US states have not approved parity for oral chemotherapy, which may place a significant financial burden on patients.

Patients should receive written educational material about the regimen, the schedule of appointments, and instructions for addressing toxicities, including emergency contact information and a clear definition of the circumstances in which the patient should contact the oncologist or another healthcare provider.²⁵ It is also recommended that patients receive written or electronic educational materials on safe handling, administration, and disposal of the drug and how to address the issue of missed doses.²⁵ Information about supportive care and the possibility of any drug-drug or drug-food interactions should also be included, if relevant.²⁵ Depending on the individual patient's ability to manage his or her own therapy, the patient's family and/or caregivers should also receive specific education about the use of oral chemotherapy.²⁵ It is critically important to tailor educational materials to a patient's reading level and to use patient feedback to gauge the patient's level of understanding and involvement.²⁵ Patient adherence and the occurrence of any potential adverse effects should be closely monitored at each visit.^{19,25}

Adverse Events and Management

It is important for oncologists to know which AEs to expect in patients with mCRC who are receiving trifluridine/tipiracil and to discuss these anticipated AEs with patients. In the RECURSE trial, hematologic AEs as well as nausea, diarrhea, vomiting, decreased appetite, and fatigue were most commonly observed in the trifluridine/tipiracil group (Table 2).⁹ These AEs most often started during the first cycle of dosing.²⁸ The recommended strategies for managing the most common hematologic and nonhematologic AEs in patients receiving trifluridine/tipiracil therapy are discussed below (Figure 2).

Hematologic Adverse Events

Myelosuppression is one of the main toxicities observed with trifluridine/tipiracil. In the RECURSE trial, the incidence of Grade 3 neutropenia was 38% in patients treated with trifluridine/tipiracil, but there was a relatively low incidence of febrile neutropenia (4%).⁹ The trifluridine/tipiracil group had a higher incidence of Grade 3 anemia (18% vs 3%) and Grade 3 thrombocytopenia (5% vs <1%) compared with the placebo group.⁹ Patients should have complete blood counts prior to receiving the drug and on day 15 of each 28-day cycle.¹⁰

Neutropenia

In the event of Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm³) within a treatment cycle, the dose of trifluridine/tipiracil should be held until the ANC rises to 1500/mm³ (Figure 2A).¹⁰ If the delay is longer than 1 week, the dose of trifluridine/tipiracil in the next cycle should be reduced by 5 mg/m²/dose from the previous dose level (Table 3).¹⁰ If febrile neutropenia occurs, the dose of trifluridine/tipiracil should be held until the episode of febrile neutropenia is completely resolved, and the drug dose in the next cycle should be reduced by 5 mg/m²/dose from the previous dose level (Table 3).¹⁰

Prophylactic administration of myeloid growth factors is recommended to prevent the development of febrile neutropenia in patients receiving myelosuppressive chemotherapy.^{29,30} The risk of febrile neutropenia is based on the patient's cancer, chemotherapy regimen, and patient factors such as age, performance or nutritional status, renal and liver function, previous chemotherapy, preexisting neutropenia or infection, and recent surgery or open wounds.^{29,30} In general, myeloid growth factors are recommended for patients with a high risk of febrile neutropenia (>20% risk), and they should be considered for those patients with an intermediate risk of febrile neutropenia (10%-20% risk).^{29,30} Currently, the myeloid growth factors approved by the US Food and Drug Administration are the granulocyte colony-stimulating factors (G-CSFs) filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim.^{29,30} Filgrastim, filgrastim-sndz, and tbo-filgrastim should be administered at 5 µg/kg/d until ANC recovery, while pegfilgrastim should be administered as a single dose of 6 mg per chemotherapy cycle.²⁹ Prophylactic antibiotics are not typically recommended for patients receiving standard-dose chemotherapy.²⁹ For patients who present with febrile neutropenia, prophylactic G-CSFs should be continued, and initiation of G-CSFs should be considered in patients who were not receiving G-CSFs prophylactically but who have risk factors for an infection-associated complication.^{29,30} With respect to trifluridine/tipiracil, G-CSF support was used in 9.4% of patients treated on the RECURSE study and nearly 27% in patients treated at one of the major centers in Japan.³¹ In patients with high-risk features^{29,30}, G-CSFs should be started once the CBC counts are known in day 15 and until the ANC rises to 2,500/mm³.³¹

Anemia

A hemoglobin level 11 g/dL should elicit an anemia evaluation (Figure 2A).³² There are many potential etiologies of anemia in patients with mCRC, including hemorrhage and nutritional deficiencies. Other conditions that may be contributing to the development of anemia should be identified and managed appropriately.³² Red blood cell transfusion is the recommended treatment for patients with symptomatic anemia due to myelosuppressive chemotherapy, and the use of transfusions should also be considered for asymptomatic patients with anemia who have underlying comorbidities, such as coronary artery disease or chronic pulmonary disease, or for those who are considered high risk.³²

Thrombocytopenia

For platelet counts <50,000/mm³, the dose of trifluridine/tipiracil should be held until the platelet counts rise to 75,000/mm³ (Figure 2A).¹⁰ If the delay is longer than 1 week, the dose of trifluridine/tipiracil in the next cycle should be reduced by 5 mg/m²/dose from the previous dose level (Table 3).¹⁰ Prophylactic platelet transfusions are recommended at a threshold platelet count of 10,000/mm³ for patients with solid tumors who have chemotherapy-induced thrombocytopenia.³³

Nonhematologic Adverse Events

In the RECURSE trial, hematologic AEs as well as nausea, diarrhea, vomiting, decreased appetite, and fatigue were most commonly observed in the TAS-102 group (Table 2).⁹ The trifluridine/tipiracil group had higher rates of Grade 3 nausea (2% vs 1%), vomiting (2% vs

<1%), and diarrhea (3% vs <1%).⁹ However, there were no clinically meaningful differences between the treatment groups in the percentage of patients with other nonhematologic AEs, including decreased appetite, stomatitis, and hand-foot syndrome.⁹ For Grade 3 nonhematologic AEs, the dose of trifluridine/tipiracil should be held until resolution of the AE to Grade 0 or 1 (Figure 2B).¹⁰ With the exception of Grade 3 nausea, vomiting, or diarrhea that is controlled by medication, the dose of trifluridine/tipiracil in the next cycle should be reduced by 5 mg/m²/dose from the previous dose level for Grade 3 nonhematologic AEs (Table 3).¹⁰

Nausea and vomiting

Chemotherapy-induced nausea and vomiting may have a substantial impact on a patient's quality of life, treatment compliance, and health status.³⁴ The goal of antiemetic therapy is to prevent the onset of nausea and vomiting, and it is important for patients to continue receiving antiemetic therapy until 2 to 3 days after the last dose of chemotherapy (when the risk of nausea and vomiting has subsided).³⁴ Recommendations for antiemetic therapy are based on the emetogenic risk of the chemotherapy agents as well as the patient's previous experience and other patient factors.^{34,35} Trifluridine/tipiracil is classified as having moderate to high emetic risk.³⁴ In the RECURSE trial, the trifluridine/tipiracil group had higher rates of severe (Grade 3) nausea (2% vs 1%) and vomiting (2% vs <1%) than the placebo group.⁹ The incidence of nausea and vomiting (any grade) in patients receiving trifluridine/tipiracil was 48% and 28%, respectively.⁹ For oral chemotherapy of moderate to high emetic risk, a 5-hydroxytryptamine 3 (5-HT₃) antagonist should be administered prophylactically (either dolasetron 100 mg/day PO, granisetron 1–2 mg/day PO, granisetron 3.1 mg/day transdermal patch, or ondansetron 16–24 mg/day PO) (Figure 2B).³⁴ A benzodiazepine (lorazepam 0.5–2 mg PO, IV, or sublingually every 6 hours as needed during the first 4 days) and/or an H₂ blocker or proton pump inhibitor may also be used as adjuncts.³⁴

Breakthrough emesis should be treated by adding a new antiemetic agent from a different class, such as a corticosteroid (dexamethasone), a cannabinoid (dronabinol or nabilone), a benzodiazepine (lorazepam or alprazolam), an atypical antipsychotic (olanzapine), or a phenothiazine (prochlorperazine or promethazine).^{34,35} After nausea and vomiting are controlled, treatment for breakthrough emesis should be administered on a prescribed schedule rather than an as-needed basis.³⁴ Patients experiencing nausea may also derive benefit from specific dietary interventions, such as: eating smaller, more frequent meals; avoiding skipping meals; limiting liquids at meals; and eating foods at room temperature.³⁴ Some studies have shown that an increased protein intake may also help curb nausea.^{36–38} Clinicians need to carefully assess nausea and vomiting throughout the entire course of treatment and determine whether the patient's antiemetic regimen is sufficient.³⁵ The cost of antiemetic treatment should also be discussed with patients, as it may have an impact on affordability and compliance.³⁵

Diarrhea

Diarrhea is a debilitating, potentially serious side effect that is commonly observed with other chemotherapy agents used in the treatment of mCRC, including 5-FU, capecitabine,

irinotecan, and oxaliplatin, when combined with fluoropyrimidine chemotherapy.³⁹ The incidence of diarrhea (any grade) in patients receiving trifluridine/tipiracil in the RECURSE trial was 32% (3% Grade 3).⁹ Diarrhea is categorized as either “uncomplicated” (Grades 1 and 2) or “complicated” (Grades 3 and 4).³⁹ The initial management of Grade 1/2 diarrhea should include modifications to the patient’s diet (small, frequent meals and elimination of lactose, alcohol, and high-osmolar supplements) and consultation with a registered dietician (Figure 2B).^{39,40} In general, for patients with Grade 1/2 diarrhea, treatment with the oral opiate loperamide hydrochloride is sufficient (4 mg initial dose followed by 2 mg every 4 hours, to a maximum of 16 mg/day) with or without diphenoxylate/atropine (1–2 tablets of 2.5/0.025 mg PO 24 times/d, to a maximum of 8 tablets/day).³⁹ For patients with persistent, Grade 3/4 diarrhea and severe dehydration, it may be necessary to administer octreotide acetate, a somatostatin analog (subcutaneously 100 to 150 µg TID or IV 25–50 µg/h) for the management of severe diarrhea and to achieve rapid control.³⁹ Intravenous fluids and treatment with an antibiotic such as a fluoroquinolone may also be required.³⁹ While the incidence of severe diarrhea is relatively low with trifluridine/tipiracil, clinicians should pay close attention to patients’ symptoms and provide early intervention with the treatment options discussed above, if warranted.

Anorexia

The incidence of severe anorexia with trifluridine/tipiracil is relatively low (4% Grade 3 in the RECURSE trial; 39% all grade).⁹ For patients who experience reduced appetite, appetite stimulants such as megestrol acetate (400–800 mg/day), dexamethasone (2–8 mg/day), or a cannabinoid should be considered (Figure 2B).⁴¹ There may also be superimposed psychological and/or emotional issues such as depression involved, and when appropriate, patients should be treated for these disorders; in the case of depression, mirtazapine (7.5–30 mg qhs) is recommended.⁴¹ The treating oncologist should also attempt to identify and address any reversible conditions (such as oropharyngeal candidiasis) or symptoms (such as dysgeusia or fatigue) that may affect food intake and contribute to anorexia.⁴¹ A nutritional consultation should be considered as should nutritional support, including liquid oral supplements as well as enteral or parenteral feeding.^{41–43} Even mild anorexia may have a significant impact on a patient’s quality of life and maintenance of appropriate body weight and may require timely intervention.

Fatigue

Although fatigue is commonly observed in patients with cancer, it is frequently underdiagnosed and undertreated.⁴⁴ The incidence of fatigue of any grade in patients receiving trifluridine/tipiracil in the RECURSE trial was 35% (4% Grade 3).⁹ With this in mind, all patients should be regularly screened for fatigue both during and after treatment.⁴⁴ In addition to medication side effects, numerous other factors may contribute to fatigue in patients with cancer, including emotional distress, anemia, sleep disturbances, nutritional problems, decreased functional status, drug-drug interactions, organ dysfunction, and other comorbidities.⁴⁴ If any of these other contributing factors is present, it should be treated appropriately (Figure 2B).⁴⁴ Patients currently receiving active treatment should use additional general intervention strategies, such as self-monitoring, energy conservation, diet, and distraction to manage their fatigue.^{44,45} Recommended nonpharmacologic interventions

include physical activity, massage therapy, and psychosocial interventions.⁴⁴ If no other causes of fatigue have been identified, the use of psychostimulants, such as methylphenidate, may be considered.⁴⁴ It may also be helpful to address any nutritional and/or sleep issues.⁴⁴

Conclusions

Trifluridine/tipiracil is a new treatment option for patients with mCRC who have been previously treated with 2 or more prior lines of standard chemotherapy, including prior fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and, in patients with *KRAS* wild-type tumors, an anti-EGFR antibody. The identification and effective management of adverse effects in patients receiving trifluridine/tipiracil are important. In particular, clinicians should be familiar with strategies to prevent and/or manage the increased incidence of myelosuppression that has been associated with trifluridine/tipiracil therapy. Moreover, communication with patients is an essential element in addressing other side effects such as nausea, vomiting, and fatigue. These strategies are critical as they may help patients stay on therapy for a longer period of time, greatly facilitate patient adherence to therapy, and ultimately improve patients' quality of life and eventual clinical outcomes.

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Abbreviations

5-FU	5-fluorouracil
5-HT₃	5-hydroxytryptamine 3
AE	adverse event
ANC	absolute neutrophil count
AST	aspartate aminotransferase
C_{max}	maximum concentration
CRC	colorectal cancer
CrCL	creatinine clearance
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FdUMP	fluorodeoxyuridine monophosphate
FdUTP	fluorodeoxyuridine triphosphate
FUTP	fluorouridine triphosphate

G-CSF	granulocyte colony-stimulating factor
HR	hazard ratio
mCRC	metastatic colorectal cancer
OS	overall survival
PFS	progression-free survival
TB	total bilirubin
TP	thymidine phosphorylase
TS	thymidylate synthase
ULN	upper limit of normal

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Figure 1.

The mechanisms of action for TAS-102 and 5-FU. 5-FU, fluorouracil; dTMP and dTTP, deoxythymidine mono- and triphosphate; dUMP, deoxyuridine monophosphate; F3dTMP, F3dTDP, and F3dTTP, trifluorodeoxythymidine mono-, di-, and triphosphate; FdUMP, fluorodeoxyuridine monophosphate; TK1, thymidine kinase 1; TPase, thymidine phosphorylase; TPI, tipiracil hydrochloride; TS, thymidylate synthase. Reprinted from Longo-Muñoz F, Argiles G, Tabernero J, et al. Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients with metastatic colorectal cancer from Spain: results of a subgroup analysis of the phase 3 RECURSE trial [published online ahead of print July 21, 2016]. *Clin Transl Oncol*. doi: 10.1007/s12094-016-1528-7.

Figure 2.

Flow charts for the management of hematological (A) and nonhematological (B) toxicities. ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor; RBC, red blood cell.

Table 1

Renal and Hepatic Function and Trifluridine/Tipiracil Treatment.

Renal Function	Classification Criteria	Trifluridine/Tipiracil Dosing
Normal	CrCL ≥ 90 mL/min or eGFR ≥ 90 mL/min/1.73 m ²	No dose adjustment
Mild Impairment	CrCL 60–89 mL/min or eGFR 60–89 mL/min/1.73 m ²	No dose adjustment
Moderate Impairment	CrCL 30–59 mL/min or eGFR 30–59 mL/min/1.73 m ²	No starting dose adjustment but may require dose modification for increased toxicity
Severe Impairment	CrCL < 30 mL/min or eGFR < 30 mL/min/1.73 m ²	Exercise caution; not recommended in EU
Hepatic Function	Classification Criteria	Trifluridine/Tipiracil Dosing
Normal	TB and AST ≤ ULN	No dose adjustment
Mild Impairment	TB ≤ ULN and AST > ULN or TB < 1 to 1.5 × ULN and any AST	No dose adjustment
Moderate Impairment	TB > 1.5 to 3 ULN and any AST	Exercise caution; not recommended in EU
Severe Impairment	TB > 3 ULN and any AST	Exercise caution; not recommended in EU

AST, aspartate aminotransferase; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; TB, total bilirubin; ULN, upper limit of normal

Table 2

Most common AEs associated with TAS-102 in patients with mCRC.⁹

Common AEs	Any Grade	Grade 3
Hematologic AE		
Neutropenia	67%	38%
Anemia	77%	18%
Thrombocytopenia	42%	5%
Nonhematologic AE		
Nausea	48%	2%
Vomiting	28%	2%
Diarrhea	32%	3%
Anorexia/decreased appetite	39%	4%
Fatigue	35%	4%

AE, adverse event; mCRC, metastatic colorectal cancer.

Table 3**Dose Modification of Trifluridine/Tipiracil (TAS-102).⁴**

Within a treatment cycle, withhold trifluridine/tipiracil (TAS-102) for any of the following:

- ANC < 500/mm³ or febrile neutropenia
 - Platelets < 50,000/mm³
 - Grade 3 or 4 non-hematologic adverse reactions
-

Do not initiate the next cycle of trifluridine/tipiracil (TAS-102) until:

- ANC ≥ 1,500/mm³ or febrile neutropenia is resolved
 - Platelets ≥ 75,000/mm³
 - Grade 3 or 4 non-hematologic adverse reactions are resolved to Grade 0 or 1
-

After recovery, resume trifluridine/tipiracil (TAS-102) at the dose reduced from the previous dose level by 5 mg/m²/dose, if the following occur:

- Febrile neutropenia
 - Uncomplicated Grade 4 neutropenia that results in more than 1 week delay in start of next cycle
 - Grade 4 thrombocytopenia that results in more than 1 week delay in start of next cycle
 - Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication
-

A maximum of 3 dose reductions is permitted to a minimum dose of 20 mg/m² twice daily. Dose escalation of trifluridine/tipiracil (TAS-102) is not permitted after it has been reduced.

ANC, absolute neutrophil count.