Metastatic Colorectal Cancer

Management with trifluridine/tipiracil

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BACKGROUND: Treatment-related adverse events (AEs) are common in patients with metastatic colorectal cancer (mCRC) receiving chemotherapy. These AEs may affect patient adherence, particularly with completely oral regimens, such as trifluridine/tipiracil (TAS-102, Lonsurf®), an antimetabolite agent for patients with mCRC refractory or intolerant to standard therapies.

OBJECTIVES: This article reviews strategies for promoting adherence and educating patients and caregivers about oral therapy with trifluridine/tipiracil.

METHODS: Recommended strategies for managing AEs are reviewed, with a focus on the most common AEs reported in patients with mCRC receiving trifluridine/tipiracil in clinical trials.

FINDINGS: Oncology nurses play an important role in educating and counseling patients regarding treatment and its potential side effects. Among patients with mCRC refractory or intolerant to standard therapies, trifluridine/tipiracil was found to have a favorable safety profile. It is associated with hematologic AEs as well as a low incidence of nausea, diarrhea, vomiting, anorexia, and fatigue.

KEYWORDS
adverse effects; trifluridine/tipiracil; TAS-102; metastatic colorectal cancer

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COLORECTAL CANCER (CRC) IS THE THIRD MOST COMMON CANCER and third most common cause of death from cancer in the United States (Siegel, Miller, & Jemal, 2015). In 2015, approximately 132,700 Americans were diagnosed with CRC and about 50,000 died from it (Siegel et al., 2015). Although mortality associated with CRC has declined in recent years and median overall survival has improved from 12 to 30 months (Kopetz et al., 2009), the five-year survival rate for patients diagnosed with distant disease is only 13% (Siegel et al., 2015). For patients with metastatic CRC (mCRC) who progress beyond first- and second-line therapies, treatment options are limited based on patients' prior therapies and *RAS* mutational status (National Comprehensive Cancer Network [NCCN], 2016c) (see Table 1). Until recently, options included retreatment with prior combination regimens, which may have been helpful if patients did not actually progress on a given agent, or regorafenib (Stivarga®), an oral multikinase inhibitor with a narrow therapeutic index.

Trifluridine/tipiracil (TAS-102, Lonsurf®) (Taiho Oncology, 2015) is a new oral therapy for treatment of mCRC and an option for patients with mCRC that is refractory to standard therapies. It is a combination of trifluridine, a thymidine based nucleic acid analog, and tipiracil, a thymidine phosphorylase inhibitor, in a 2:1 molar ratio, leading to a prolonged half-life of trifluridine and allowing twice-daily dosing (Emura, Suzuki, Fujioka, Ohshimo, & Fukushima, 2005; Temmink, Emura, de Bruin, Fukushima, & Peters, 2007). The mechanism of action of trifluridine/tipiracil is distinct from that of 5-fluorouracil (5-FU), a uracil-based analog, which is the cornerstone of mCRC treatment (Longley, Harkin, & Johnston, 2003; Wilson, Danenberg, Johnston, Lenz, & Ladner, 2014). Preclinical studies demonstrate that 5-FU–resistant tumors are still sensitive to trifluridine/tipiracil (Emura, Murakami, Nakagawa, Fukushima, & Kitazato, 2004). At the current dosing schedule, the cytotoxic effect of trifluridine/tipiracil is mediated primarily through incorporation of trifluridine into DNA, substituting for thymidine, leading to DNA base replication and chain termination errors (Sakamoto et al., 2015; Tanaka et al., 2014; Temmink et al., 2007).

Efficacy and safety of trifluridine/tipiracil in patients with mCRC refractory or intolerant to standard therapies were evaluated in the phase 3 RECOURSE trial; enrollment criteria included two or more prior lines of standard chemotherapy (including fluoropyrimidine [5-FU], oxaliplatin [Eloxatin®], irinotecan