Adverse Event Management Strategies: Optimizing Treatment With Regorafenib in Patients With Metastatic Colorectal Cancer

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Patients with metastatic colorectal cancer (mCRC) frequently experience treatment-related adverse events (AEs), which may lead to nonadherence or discontinuation from their treatment regimen. In the phase 3 CORRECT study, the addition of regorafenib to best supportive care (BSC) significantly increased overall survival and progression-free survival compared with placebo plus BSC in patients with mCRC who had progressed on all approved standard care therapies. Although regorafenib showed an acceptable safety profile, patients experienced treatment-related AEs such as hand-foot skin reaction, hypertension, oral mucositis, diarrhea, fatigue, and liver abnormalities. The goal of this article is to help oncology nurses implement a strategic, proactive approach to AE management in patients mCRC treated with regorafenib. The article reviews the most common AEs associated with regorafenib in patients who participated in the CORRECT study and provides a strategy and practical measures that nurses can apply to AE management. In addition, the article provides direction and guidance for educating patients and their caregivers on recognizing and managing potential side effects of regorafenib.
TABLE 1. Incidence of Treatment-Related Adverse Events Occurring in 10% or More of the Patients Enrolled in the CORRECT Study (N = 753)

<table>
<thead>
<tr>
<th>Clinical Adverse Event</th>
<th>Regorafenib (n = 500)</th>
<th>Placebo (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>237</td>
<td>47</td>
</tr>
<tr>
<td>Hand-foot skin reactions</td>
<td>233</td>
<td>47</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>169</td>
<td>34</td>
</tr>
<tr>
<td>Anorexia</td>
<td>153</td>
<td>30</td>
</tr>
<tr>
<td>Voice changes</td>
<td>147</td>
<td>29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>139</td>
<td>28</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>136</td>
<td>27</td>
</tr>
<tr>
<td>Rash or desquamation</td>
<td>130</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>72</td>
<td>14</td>
</tr>
<tr>
<td>Weight loss</td>
<td>69</td>
<td>14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Fever</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyperbilirubinemia</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>• Increased AST</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>• Increased ALT</td>
<td>27</td>
<td>5</td>
</tr>
</tbody>
</table>

ALT—alanine aminotransferase; AST—aspartate aminotransferase; NA—not applicable
Note. The liver function test abnormalities reported in the table occurred in 5% or more of the patients.
Note. Based on information from Grothey et al., 2013a.

Proactive Adverse Event Management

In the CORRECT trial, the most frequently observed treatment-related AEs of any grade occurring in at least 10% of patients receiving regorafenib included fatigue, hand-foot skin reactions (HFSRs), diarrhea, anorexia, voice changes, hypertension, and oral mucositis (Grothey et al., 2013a). In addition, increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hyperbilirubinemia were observed in some patients (Bayer HealthCare, 2013) (see Table 1). However, the discontinuation rate of regorafenib-treated patients from treatment-related AEs (not associated with disease progression) was low (8% versus 3% in the placebo group) (Bayer HealthCare, 2012), suggesting that many AEs can be managed. A strategic proactive approach to AE management was required by the CORRECT study protocol, which included stringent patient monitoring, proactive supportive measures, and frequent clinical visits early in the initiation of therapy (Bayer HealthCare, 2012).

Many treatment-emergent AEs, including HFSR, hypertension, liver abnormalities, fatigue, diarrhea, and oral mucositis, occurred early in the course of treatment, during cycles 1 and 2, and their incidence decreased during subsequent treatment cycles. In addition to a proactive approach to AE management, some treatment-related AEs may require specific regorafenib dose modifications or dose interruptions. In the CORRECT study, the regorafenib daily dose was usually reduced during treatment cycles 2 and 3, as the dose was adjusted to manage treatment-related AEs (Grothey et al., 2013b). After treatment cycle 3, the regorafenib dose remained relatively stable.

Hand-Foot Skin Reactions

HFSRs usually occur on skin surfaces where pressure or friction occurs, such as the palms of the hands, tips of the fingers...
and toes, and soles and heels of the feet (Lacouture et al., 2008; Wood et al., 2010). HFSRs are characterized by asymmetric, localized hyperkeratotic lesions that may be surrounded by erythematous regions. Initially, the affected areas become scaly and erythema may develop. The scaly lesions may blister and, after several weeks, a painful thickening of the skin may occur, which may interfere with the patient’s ability to perform normal activities of daily living (see Table 2). In the CORRECT trial, 47% of patients treated with regorafenib experienced any grade HFSR, mainly grades 1 and 2, compared with 8% of patients who received placebo. A total of 83 (17%) patients experienced grade 3 HFSR and no patients experienced grade 4 HFSR (Grothey 2013a). No evidence-based treatment for HFSR from regorafenib is available. Most cases of HFSR in patients treated with regorafenib appeared during the first cycle of treatment (Bayer HealthCare, 2013). Therefore, proactive patient education and reinforcement of supportive measures are critical for the management of HFSRs.

Nursing considerations: HFSRs occur early in the course of treatment, mainly during cycle 1, and potentially can be prevented or managed by strategic proactive measures (see Figure 1). Patient education on the practical measures that potentially may prevent or lessen the severity of HFSRs should be started before treatment initiation and continue throughout the treatment course. Patients should be screened and monitored weekly during the first treatment cycle (four weeks). During this time, if no evidence of HFSRs exist, then screen once every two weeks. Before any visible signs of HFSRs occur in the feet, patients may complain of pain and discomfort while walking. Nurses could recommend that patients report HFSRs via phone or email.

Several proactive measures are available to the patient. First, patients should soften and remove any preexisting calluses on their hands and feet prior to and during treatment. In addition to controlling calluses, patients are encouraged to use non–urea-based moisturizing creams regularly to soften the skin on the hands and feet. If a callus begins to form, the use of keratolytic creams containing urea, salicylic acid 6%, or alpha-hydroxyl acid to gently exfoliate callused skin may help. Because calluses develop as a result of pressure, nurses should instruct patients on the importance of protecting pressure points or irritated areas on the hands and feet. Patients should use thick cotton socks and gloves, wear well-fitted, padded shoes, and avoid clothing that rubs or irritates the skin. Wearing proper-fitting shoes with padded insoles to reduce pressure and rubbing on toes and feet and using padded gloves when engaging in activities that may damage the skin on the hands will help prevent callus formation. Daily foot soaks in warm water with magnesium sulfate will soften callused tissue and make it easier to remove. If calluses cause pain on walking, the thickened skin can be removed by a podiatrist. In addition to the supportive measures and practical recommendations discussed here, some patients may require regorafenib dose modifications or interruptions to effectively manage their HFSRs. For these patients, dose reduction and/or temporary interruption of regorafenib, or in severe or persistent cases, discontinuation of regorafenib, should be considered. Guidelines for modifying the regorafenib dose in patients with HFSRs are presented in Table 3.

Hypertension

In the CORRECT trial, hypertension was reported in 28% of patients treated with regorafenib compared with 6% of those treated with placebo (Grothey et al., 2013a). In most patients, the onset of hypertension occurred during the first cycle of regorafenib treatment.

Nursing considerations: For all patients starting regorafenib, blood pressure (BP) should be measured and adequately controlled before treatment initiation. After starting regorafenib treatment, patients should be screened and monitored weekly during the first cycle (four weeks). During this time, if no evidence of elevated BP exists, then screening should be reduced to once every two weeks. If grade 1 hypertension is noted in the clinic, then patients need to be advised to have a monitor at home to check BP daily. Patients should keep a log of their daily BP readings and notify the healthcare team of any elevations. Blood pressure out of normal range is systolic 140 mmHg or greater and diastolic 90 mmHg or greater (or a 20 mmHg or greater diastolic increase if previously within normal limits). If high BP develops during regorafenib treatment, several classes of oral antihypertensive agents can be prescribed to manage hypertension (Albert, 2005). In addition to careful BP monitoring and review of the antihypertensive medications, several proactive measures can be taken to manage hypertension.

Control of Calluses

Before initiating treatment with regorafenib

- Check condition of hands and feet.
- Suggest a manicure or pedicure, when indicated.
- Recommend pumice stone for callus or “rough spot” removal.

During regorafenib treatment

- Avoid pressure points.
- Avoid items that rub, pinch, orcreate friction.

Use of Creams

- Non–urea-based creams: Apply liberally to soften skin of hands and feet.
- Keratolytic creams (urea-based creams, salicylic acid 6% cream): Use sparingly and apply only to affected (hyperkeratotic) areas.
- Alpha-hydroxyl acid-based creams (about 5%–8%): Apply liberally two times each day.
- For pain control, consider topical analgesics such as lidocaine 2%.
- For patients with grade 2 or 3 hand-foot skin reactions, consider topical corticosteroids such as clobetasol 0.05%.
- Avoid systemic steroids.

Cushions

Protect tender areas.

- Use socks or gloves to cover moisturizing creams.
- Wear well-padded footwear.
- Use insole cushions or inserts (silicon or gel).
- Foot socks with tepid water and Epsom salts

FIGURE 1. Proactive Measures for the Management of Hand-Foot Skin Reactions

Note. Based on information from Bayer HealthCare, 2012; Lacouture et al., 2008.
regimen, some patients with regorafenib-related hypertension might require regorafenib dose modifications. General recommendations for the management of hypertension in patients receiving regorafenib are presented in Table 4.

Liver Abnormalities

In the CORRECT trial, changes in ALT, AST, and bilirubin levels were usually observed early in the course of treatment, during cycles 1 and 2 (Grothey et al., 2013a). Although a higher incidence of elevated ALT, AST, and bilirubin levels were noted in patients treated with regorafenib compared with placebo, the difference was mainly from grade 1 and 2 AEs (Grothey et al., 2013a). Severe liver function test abnormalities (grade 3 or 4) or hepatic dysfunction were observed in a small number of patients (Grothey et al., 2013a).

Nursing considerations: Since liver-related abnormalities have been observed in some patients during treatment with regorafenib, patients should undergo careful monitoring of liver function prior to and during regorafenib treatment. Liver function tests (ALT, AST, bilirubin) should be performed before initiation of treatment with regorafenib and monitored closely—at least every two weeks—during the first two months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Nurses should advise patients to avoid acetaminophen or acetaminophen-based medications and review medications taken by the patient that can cause increasing liver function abnormalities, such as antilipids. In addition to active patient monitoring and early detection, effective management of treatment-related liver function abnormalities might require specific changes in the regorafenib dose or an interruption in the treatment schedule. Guidelines for modifying the regorafenib dose in patients with abnormal liver function are presented in Tables 5 and 6.

Oral Mucositis

In the CORRECT trial, 27% of patients treated with regorafenib experienced oral mucositis compared with 4% of patients who received placebo (Grothey et al., 2013a). The signs and symptoms of oral mucositis included pain, erythema, and ulceration, which can lead to infection, malnutrition, and dehydration (Peterson, Keefe, & Sonis, 2012). Because most cases of oral mucositis appeared during the first cycle of treatment, proactive patient education and supportive measures are needed at treatment initiation and during the course of treatment.

Nursing considerations: Patients should be educated on the basic daily oral care that they should undertake to reduce the risk or severity of oral mucositis (see Figure 2). Hydration of the oral mucosa may help reduce the severity of oral mucositis and can be recommended as part of the patient’s daily oral care. Since patients with oral mucositis may have difficulty chewing food and swallowing, they should be screened for nutritional risk. Enteral nutrition may be considered if a risk exists for malnutrition and weight loss. Regularly monitor for oral pain to minimize weight loss among patients experiencing this condition. Depending on the degree of mucosal injury, patient-controlled analgesia with morphine or topical anesthetics may be used to provide pain relief (Peterson, Bensadoun, & Roila, 2011; Wood et al., 2010). In addition to supportive measures, effective management may require regorafenib dose modifications to prevent recurrent severe mucositis.

Diarrhea

In the CORRECT trial, 34% of the regorafenib-treated patients experienced diarrhea (mainly grade 1 and 2) compared with 8% of patients receiving placebo (Grothey et al., 2013a). Treatment-related diarrhea must be treated promptly to avoid dehydration; early intervention may be necessary in some

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Maintain dose level and immediately institute supportive measures for symptomatic relief</td>
<td>Consider decreasing dose by one tablet (40 mg) mg and immediately institute supportive measures. If no improvement is noted, interrupt therapy for a minimum of seven days until toxicity resolves to grade 0 or 1. A dose re-escalation is permitted at the discretion of the treating physician.</td>
<td>Institute supportive measures immediately. Interrupt therapy for a minimum of seven days until toxicity resolves to grade 0 or 1. When resuming treatment, decrease the dose by one tablet (40 mg). A dose re-escalation is permitted at the discretion of the treating physician.</td>
</tr>
<tr>
<td>Second (or no improvement within seven days)</td>
<td>–</td>
<td>Interrupt therapy for a minimum of seven days until toxicity resolves to grade 0 or 1. When resuming treatment, decrease the dose by one tablet (40 mg). A dose re-escalation is permitted at the discretion of the treating physician.</td>
<td>Institute supportive measures immediately. Interrupt therapy for a minimum of seven days until toxicity resolves to grade 0 or 1. When resuming treatment, decrease the dose by one tablet (40 mg).</td>
</tr>
<tr>
<td>Third</td>
<td>–</td>
<td>Interrupt therapy until toxicity resolves to grade 0 or 1. When resuming treatment, decrease the dose by one tablet (40 mg). A dose re-escalation is permitted at the discretion of the treating physician.</td>
<td>Discontinue treatment immediately.</td>
</tr>
</tbody>
</table>

Note. Based on information from Bayer HealthCare, 2012.

*The recommended regorafenib dose is 160 mg (four 40 mg tablets) daily for three weeks.
patients (Schwandt, Wood, Rini, & Dreicer, 2009; Stein, Voigt, & Jordan, 2010).

**Nursing considerations:** Initial management of diarrhea may include the use of antidiarrheal medications, such as loperamide, octreotide, and tincture of opium, which can be started at the first signs of diarrhea and continued as needed (Stein et al., 2010). In addition to the use of antidiarrheal agents, educate patients about the dietary modifications they can undertake to better manage their diarrhea (Benson et al., 2004). Patient adherence to dietary recommendations along with the use of antidiarrheal medications, when needed, may provide adequate diarrhea control and lessen the need to reduce the dose of regorafenib or discontinue treatment.

**Fatigue**

In the CORRECT trial, 47% of patients treated with regorafenib and 28% of those treated with placebo experienced fatigue (Grothey et al., 2013a). The cause of fatigue is not fully understood, making it difficult to determine if a patient’s fatigue is disease or drug related. Before attributing fatigue to cancer or its treatment, the patient should be monitored closely for underlying physiological and psychological causes of fatigue (Schwandt et al., 2009).

**Nursing considerations:** Nurses should take a proactive approach and regularly monitor patients for fatigue. Causes of fatigue, such as pain, anemia, or hypothyroidism, all are conditions that can improve with medical treatment. Closely monitoring patients for fatigue also can identify psychological causes of fatigue such as clinical depression, which can be treated with patient support measures and, if needed, pharmacologic therapy. Monitor patients for proper nutrition and hydration. For patients with nutritional deficiencies, implement measures that ensure the patient is consuming enough fluids, calories, and protein, which may help reduce fatigue. In general, early interventions can improve the patients’ quality of life and enable them to continue their treatment.

**Other Adverse Effects**

Treatment with regorafenib also has been associated with laboratory abnormalities such as high levels of thyroid stimulating hormone, elevated lipase, and hypophosphatemia (Grothey et al., 2013a). If thyroid function tests are consistent with hypothyroidism, treat appropriately; monitor thyroid function closely

### TABLE 4. Management of Hypertension With Regorafenib Dose Modifications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Blood Pressure</th>
<th>Antihypertensive Therapy</th>
<th>Recommended Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prehypertension (systolic, 120–139 mmHg; diastolic, 80–89 mmHg)</td>
<td>None</td>
<td>Continue regorafenib. Consider blood pressure monitoring.</td>
</tr>
<tr>
<td>2</td>
<td>Systolic, 140–159 mmHg; diastolic, 90–99 mmHg or symptomatic increases by greater than 20 mmHg (diastolic) if previously within normal limits</td>
<td>Treat with the aim to achieve diastolic of 90 mmHg or lower. If blood pressure was previously within normal limits, start antihypertensive monotherapy. If the patient is already on antihypertensive medication, titrate up the dose.</td>
<td>Continue regorafenib. If symptomatic, hold regorafenib until symptoms resolve and diastolic blood pressure is 90 mmHg or lower. When regorafenib is restarted, continue at the same regorafenib dose level.</td>
</tr>
<tr>
<td>3</td>
<td>Systolic, 160 mmHg or greater; diastolic, 100 mmHg or greater or more than one antihypertensive drug or more intensive therapy than previously indicated</td>
<td>Treat with the aim to achieve diastolic of 90 mmHg or lower. Start antihypertensive medication and/or increase current antihypertensive and/or add additional antihypertensive medications.</td>
<td>Hold regorafenib until diastolic blood pressure is 90 mmHg or lower and, if symptomatic, until symptoms resolve. When regorafenib is restarted, continue at the same regorafenib dose level. If blood pressure is not controlled with the addition of new or more intensive therapy, reduce by one dose level. If grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)</td>
<td>—</td>
<td>Discontinue regorafenib therapy.</td>
</tr>
</tbody>
</table>

*Note. Based on information from Bayer HealthCare, 2012.*

### TABLE 5. Grading of Liver Function Abnormalities

<table>
<thead>
<tr>
<th>Grade</th>
<th>ALT or AST</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; ULN–3 x ULN</td>
<td>&gt; ULN–1.5 x ULN</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 3–5 x ULN</td>
<td>&gt; 1.5–3 x ULN</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 5–20 x ULN</td>
<td>&gt; 3–10 x ULN</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 20 x ULN</td>
<td>&gt; 10 x ULN</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ALT—alanine aminotransferase; AST—aspartate aminotransferase; NA—not applicable; ULN—upper limit of normal
Implications for Practice

- Educate patients with metastatic colorectal cancer about common adverse events (AEs) experienced with regorafenib treatment, including hand-foot skin reactions, hypertension, oral mucositis, diarrhea, and fatigue.
- Use a proactive strategy with an emphasis on patient and caregiver education. AEs associated with regorafenib generally are manageable if these steps are applied early in the course of treatment.
- Provide support services offering ongoing education and guidance on the management of side effects to patients with metastatic colorectal cancer starting treatment with regorafenib.

(at least every two weeks) until levels are stabilized and periodically thereafter or as clinically indicated.

In the CORRECT trial, hypophosphatemia was reported in 5% of patients receiving regorafenib compared with less than 1% of patients receiving placebo (Grothey et al., 2013a). Phosphorus and lipase levels in the blood should be measured at baseline and monitored frequently during initial cycles of treatment and throughout the course of treatment, as some patients may require dose modifications or dose interruptions at some point during therapy.

Recommended Dosing and Administration

The recommended regorafenib dose is 160 mg (four 40 mg tablets daily) (Bayer HealthCare, 2013). This dose should be taken orally with a low-fat meal once daily for the first 21 days of each 28-day cycle (no regorafenib tablets are taken on days 22–28). Regorafenib tablets should be stored at room temperature, between 68°F and 77°F, in the bottle they came in, and not in a daily or weekly pill box. The desiccant should be kept in the bottle and the bottle tightly closed. Any unused regorafenib tablets after 28 days of opening the bottle should be discarded in accordance with local requirements.

The Resources for Expert Assistance and Care Helpline® (REACH®) support program is an important resource for patients starting therapy. REACH reimbursement counselors can assist with evaluating patient insurance coverage and providing reimbursement support. REACH nurse counselors are available 24 hours a day, 365 days a year, and offer ongoing education and support to patients taking regorafenib by answering questions and providing guidance on managing side effects. Another valuable resource for patients starting therapy is a patient treatment journal. The journal provides a simple format for patients to record how they are feeling and how many pills they take each day. Patients also can record their BP measurements, their skin-care needs, and other issues they wish to discuss with the nursing team. Patients should be encouraged to use the journal daily and bring it to their next clinical appointment as this information can help determine if dose modification or other supportive measures are needed.

Conclusions

Regorafenib, a newly approved oral multikinase inhibitor for the treatment of mCRC, has shown clinical efficacy as monotherapy by prolonging life in heavily pretreated patients who have limited available treatment options. Overall, the AEs associated with regorafenib are manageable if the proactive approach emphasized by the CORRECT protocol is applied in clinical practice. This proactive strategy includes stringent patient monitoring, proactive support measures, and frequent clinic visits early in the initiation of regorafenib therapy. Nurse, patient, and caregiver education is critical to ensure increased awareness of potential side effects of regorafenib and the need to alert the healthcare team of early signs of AEs. Overall, proactive AE management may improve patients’ treatment experience and maximize patient adherence, allowing patients to be treated with regorafenib without compromising its clinical efficacy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ALT and/or AST Elevations</th>
<th>Occurrence</th>
<th>Recommended Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or lower</td>
<td>≤ 5 x ULN</td>
<td>Any occurrence</td>
<td>Continue treatment. Monitor liver function weekly until transaminases return to &lt; 3 x ULN (grade 1) or baseline.</td>
</tr>
<tr>
<td>2 or higher</td>
<td>&gt; 3 x ULN</td>
<td>Any occurrence&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Discontinue treatment permanently. Monitor liver function weekly until resolution or return to baseline.</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 5 x ULN to ≤ 20 x ULN</td>
<td>First occurrence</td>
<td>Interrupt treatment. Monitor transaminases weekly until levels return to &lt; 3 x ULN or baseline. Patients may restart treatment if the potential risk outweighs the risk of liver toxicity. To restart treatment, reduce dose by one tablet (40 mg) and monitor liver function weekly for at least four weeks. Discontinue treatment permanently.</td>
</tr>
<tr>
<td>4</td>
<td>≥ 20 x ULN</td>
<td>Any occurrence</td>
<td>Discontinue treatment permanently.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Exception patients with Gilbert’s syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

ALT—alanine aminotransferase; AST—aspartate aminotransferase; ULN—upper limit of normal

Note. Based on information from Bayer HealthCare, 2012.
Oral Mucositis
Educate patients on basic daily oral care.
- Use soft tooth brushes and gentle toothpaste.
- Use warm non-medicated oral rinses (saline, baking soda) twice daily.
- Avoid alcohol-based mouth rinses.
Screen for nutritional risk.
- Patients may have difficulty chewing and swallowing.
- Consider enteral nutrition if at risk of malnutrition or weight loss.
Use of analgesics or topical anesthetics
- If needed, a patient-controlled analgesia with morphine or topical anesthetics may be used for pain relief.
Regorafenib dose modification may be required to prevent recurrent severe mucositis.

Diarrhea
Use of antidiarrheal medications may be necessary at first signs of diarrhea.
Educate patients on the following.
- Drink at least eight glasses of clear fluid daily to prevent dehydration.
- Eat small, frequent meals.
- Add more high-soluble fiber foods to diet, such as bananas and rice.
- Avoid high-insoluble foods such as fresh fruit, raw vegetables, alcohol, and dairy products.
Regorafenib dose modification may be required if diarrhea is persistent and severe.

Fatigue
Identity correctable causes of fatigue, such as pain, anemia, and hypothyroidism. May improve with medical treatment.
Monitor patients for the following.
- Signs and symptoms of clinical depression
- Proper nutrition and hydration
Regorafenib dose modification may be required if fatigue is severe.

FIGURE 2. Recommended Measures for Management of Oral Mucositis, Diarrhea, and Fatigue
Note. Based on information from Benson et al., 2004; Peterson et al., 2011; Schwandt et al., 2009; Stein et al., 2010.

References