An Oncology Nurses’ Guide to New Targeted Agents for Metastatic Colorectal Cancer

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Background: Colorectal cancer (CRC) that has metastasized before being discovered, or reoccurs following surgery, remains a major treatment challenge. Trials have established the usefulness of antiangiogenic agents and new regimens in prolonging survival in patients with advanced disease. In the United States, the antiangiogenic agents approved for treating metastatic CRC often are combined with traditional chemotherapeutic agents and include bevacizumab (Avastin®), ziv-aflibercept (Zaltrap®), and regorafenib (Stivarga®).

Objectives: This article reviews factors that guide the development of a nursing plan for monitoring and managing patients who are receiving antiangiogenic therapies.

Methods: Regorafenib and ziv-aflibercept, two newer agents that nurses and other healthcare professionals may have had less experience with, were reviewed.

Findings: The key to maximizing the potential benefit of these agents is understanding where these new therapies fit in the overall scheme of treatment options and how to help patients tolerate treatment.

C olorectal cancer (CRC) often is curable if detected before it metastasizes, with surgical resection resulting in a cure in about 50% of patients (National Cancer Institute [NCI], 2013). However, metastatic CRC (mCRC) and recurrent CRC remain major treatment challenges. A tumor needs new blood vessels to receive the nutrients and oxygen necessary for growth. The development of new blood vessels is called angiogenesis. The class of targeted therapies known as antiangiogenic agents works by blocking the growth of blood vessels to tumors. Trials have established the usefulness of antiangiogenic agents and new regimens in prolonging the survival of patients with advanced disease (National Comprehensive Cancer Network [NCCN], 2014; Smaglo & Hwang, 2013). In particular, two new agents, ziv-aflibercept (Zaltrap®) and regorafenib (Stivarga®), have been approved for use in specific situations. Although these agents target angiogenesis, significant differences exist between them (see Figure 1). Bevacizumab (Avastin®) is a specific inhibitor of vascular endothelial growth factor (VEGF)–A, whereas ziv-aflibercept and regorafenib inhibit multiple VEGF ligands or receptors, respectively. Regorafenib additionally inhibits many other receptor tyrosine kinases. The complexity of the angiogenesis process presents a pathway with multiple targets that can be disrupted (Jitawatanarat & Wee, 2013; Saif, 2013; Sun, 2012). These newer agents have multiple targets, increasing the chance for successful angiogenesis inhibition and the potential for additional treatment-related side effects (Jitawatanarat & Wee, 2013; Saif, 2013).

Monitoring, Side-Effect Prevention, and Patient Education

When managing patients with mCRC who are being treated with any of the antiangiogenic targeted therapies, creating a nursing plan to assess for adverse events (AEs), minimize the occurrence and severity of side effects, and provide management...
strategies is vitally important (Rieger & Yarbro, 2003). If toxicities can be proactively managed, the risk of dose reduction, dose delay, or termination of therapy can be minimized. Other agents, such as cytotoxic drugs, may be a part of these regimens and the interactions and AEs of multiple drugs need to be considered when developing the nursing plan.

Patient education is a key component of effective nursing care (Grenon, 2013; Rieger & Yarbro, 2003). To alert patients about what to expect during treatment with antiangiogenic drugs, nurses can educate patients about the benefits of treating side effects early, rather than waiting until they become more severe. Some patients may be reluctant to report mild side effects because of the fear that therapy will be terminated and they may run out of treatment options. Therefore, a crucial component of patient education is to convey that early treatment of AEs can, in fact, prolong the length of time that therapy may be continued.

Talking With Patients About Regorafenib

In clinical trials with regorafenib, treatment-related AEs were seen in 93% of the patients in the regorafenib group versus 61% of patients who received the placebo (Grothey et al., 2013). Grade 3 or higher AEs, considered to be related to regorafenib, were hand-foot skin reactions, fatigue, diarrhea, hypertension, and rash or desquamation. Common all-grade AEs include hand-foot skin reactions, rash or desquamation, fatigue, diarrhea, hypertension, mucositis, hemorrhage, infection, weight loss, increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, thrombocytopenia, and lymphopenia (American Society of Health-System Pharmacists [ASHSP], 2013; Grothey et al., 2013). Treatment-related AEs leading to death with regorafenib use included pneumonia, gastrointestinal bleeding, intestinal obstruction, pulmonary hemorrhage, seizures, sudden death, and hepatotoxicity, whereas pneumonia and sudden death also were seen in the placebo group. AEs were the most frequent cause of dose modification. In the regorafenib group, 76% of the patients needed dose modification, and, of those, 20% needed one or more dose reductions and 70% required one or more dose interruptions. In the placebo group, 38% of patients needed dose modifications. However, despite the higher rate of AEs in patients who received regorafenib, patients in both groups (treatment and placebo) reported similar changes in quality of life.

Emphasizing the importance of proper adherence to the regimen is a critical element of nursing care. Nurses should encourage patients to call their doctor’s office immediately if they experience certain side effects, particularly those related to hepatotoxicity and bleeding (ASHSP, 2013). In addition, patients should promptly inform the clinician of any other side effects, such as weight loss, pain and inflammation in the mouth, or redness or soreness on the hands or feet. It may be helpful to have a handout to send home with the patient after educational sessions (see Figure 2). It also is important to let patients know that dose reductions and delays might occur with regorafenib. Patients should be reassured that those decisions will be made with their doctor, and that they should continue to take the medication as instructed. Patients using regorafenib should be instructed to take their medication with a low-fat breakfast and not to eat grapefruit or drink grapefruit juice while they are on regorafenib (ASHSP, 2013).

Talking With Patients About Ziv-Aflibercept

Infrequent but serious side effects are associated with ziv-aflibercept; therefore, patients should know that many of these effects should be addressed immediately (Sanofi-Aventis, 2012).
Some of the more serious complications seen in patients who were treated with ziv-aflibercept included those related to bleeding, such as nosebleeds, bleeding gums, coughing up or vomiting blood, blood in the stool or urine, or splitting open of a wound that has closed (i.e., dehiscence) (Sanofi-Aventis, 2012). In clinical trials with ziv-aflibercept, grade 3 and 4 AEs were reported in 84% of the ziv-aflibercept group and 63% of patients receiving placebo (Van Cutsem et al., 2012). Of note, grade 3 and 4 hypertension, arterial and venous thrombotic events, diarrhea, asthenic conditions, stomatitis and ulceration, infections, and palmar-plantar erythrodysesthesia were significantly higher in the ziv-aflibercept arm. Severe and sometimes fatal AEs, including gastrointestinal perforation or fistula formation, compromised wound healing, arterial thrombotic events, and reversible posterior leukoencephalopathy syndrome, have been reported in patients receiving ziv-aflibercept (Van Cutsem et al., 2012). Discontinuation of study participation due to AEs was required for 27% of patients receiving ziv-aflibercept and 12% of patients receiving placebo (Van Cutsem et al., 2012). Because gastrointestinal perforations have been known to occur with ziv-aflibercept (0.8% grade 3/4 versus 0.2% with placebo), patients must be made aware of the symptoms, such as abdominal pain, constipation, nausea, vomiting, and fever (Sanofi-Aventis, 2012).

As was previously recommended for regorafenib, it may be helpful to have a prepared handout that outlines some of the more serious complications associated with ziv-aflibercept (see Figure 3). Overall, the most common side effects seen in patients treated with ziv-aflibercept include proteinuria, hypertension, hemorrhage, nosebleed, diarrhea, asthenia, fatigue, headache, stomatitis, infections, abdominal pain, infection, weight loss, hand-foot syndrome, increased ALT or AST levels, thrombocytopenia, leukopenia, and neutropenia (Sanofi-Aventis, 2012; Van Cutsem et al., 2012). Prior to initiating treatment with ziv-aflibercept, healthcare providers should determine whether the patient has had any recent surgeries and whether any surgeries are planned, as treatment with ziv-aflibercept cannot be started for at least 28 days after surgery and must be paused for at least 28 days before any planned surgery (Sanofi-Aventis, 2012).

Monitoring and Treatment of Selected Toxicities

Nurses should carefully monitor patients while they are receiving any antiangiogenic therapy, particularly during the first four weeks of treatment (Eisen et al., 2012). Monitoring should include office visits during which earlier education can be reinforced and side effects can be discussed and assessed. In addition, nurses should ensure that all appropriate laboratory tests are being ordered, such as urine dipstick, urinary protein creatinine ratio, complete blood count with differential, and serum AST and ALT. In addition, patients should be monitored for signs and symptoms of hypertension, bleeding, and thromboembolic events. Evidence from clinical trials has indicated that, for patients taking regorafenib or ziv-aflibercept, the overall discontinuation rates related to AEs were low, suggesting that many AEs can be managed with treatment or dose reduction (Grothey et al., 2013; Van Cutsem et al., 2012).

Hand-Foot Skin Reaction of Regorafenib Versus Ziv-Aflibercept

Skin toxicities are frequently seen in patients receiving targeted cancer therapies and are a significant potential cause of dose reductions and delays (Belum, Wu, & Lacouture, 2013; Grenon, 2013). Evidence shows that preemptive attention and careful management can prevent such dose reductions or delays, and can have a positive impact on patient outcomes. One essential point that is not well recognized is that hand-foot skin reactions and hand-foot syndrome are not the same entities (Hagopiana & Packera, 2010; Son, Lee, Lee, Yun, & Chun, 2009) (see Table 1). However, the grading scale (see Table 2) and management strategies (see Figure 4) used to assess severity are the same (BC Cancer Agency, 2013; NCI, 2010).

Hand-foot skin reactions are characterized by scaling surrounded by erythema and are found on the pressure-bearing areas of the hands and feet (Urban & Anadkat, 2013). Patients with hand-foot skin reactions present with pain, dysesthesia, and palmar and plantar hyperkeratotic plaques with an acral distribution, affecting distal portions of limbs (e.g., hand, foot) (Hagopiana & Packera, 2010). Compared with hand-foot syndrome, hand-foot skin reactions are characterized by more callous formation, blistering, sloughing, and tender reaction.

Reminders about your treatment with regorafenib (Stivarga®)

This oral medication must be taken exactly as instructed by your doctor or nurse. Swallow the tablets whole—do not split, chew, or crush them. Do not eat grapefruit or drink grapefruit juice while taking this medication. Otherwise, continue to eat what you would normally eat unless your doctor tells you to make changes to your diet.

This medication must be taken with a low-fat breakfast. Examples of low-fat breakfast items include:
- White toast with low-fat margarine or jelly
- Skim milk
- Cereal or oatmeal
- Apple juice
- Coffee or tea.

Tell your doctor if you have any side effects from regorafenib.

Call your doctor immediately if you experience:
- Yellowing of the skin or eyes
- Nausea or vomiting
- Flu-like symptoms
- Dark-colored urine
- Pain in the upper right part of the abdomen (stomach area)
- Extreme tiredness or lack of energy
- Unusual bleeding or bruising
- Loss of appetite
- Change in sleep habits.

Also, be on the lookout for weight loss, pain and inflammation of gums or in the mouth, and redness or soreness on the hands or feet. Talk with your doctor if any of these occur.

Note. This document is a sample. Check with your institution for additional drug-specific patient information.

FIGURE 2. Handout for Patients Taking Regorafenib: Sample Language
Hand-foot syndrome is most often associated with chemotherapeutic agents such as capcitabine (Afinitor®), doxorubicin (Adriamycin®) and liposomal doxorubicin (Doxil®), cytarabine (Cytosar-U®), docetaxel (Taxotere®), and 5-fluorouracil (Adrucil®), but also is seen with some targeted therapies including ziv-aflibercept, regorafenib, sorafenib (Nexavar®), and sunitinib (Sutent®) (Grenon, 2013; Grothey et al., 2013; Lacouture et al., 2013; Reilly, Gerami, & Guitart, 2008; Nagore, Insa, & Sanmartin, 2000; Van Cutsem et al., 2012). Hand-foot syndrome is a dermatologic toxicity affecting the growth of skin cells and is characterized by redness and pain on the palm of the hand and sole of the foot (Gomez & Lacouture, 2011). It presents as a diffuse redness, tenderness, dryness, cracking, and hyperpigmentation—particularly in patients with darker complexions (Son et al., 2009). Hand-foot skin reactions can progress rather quickly, whereas hand-foot syndrome may be more indolent. Both seem to be dose dependent, which is why education, early assessment, and proactive management, including dose reductions, are key.

Hand-foot skin reaction is a known side effect of multikinase inhibitors, seen in 34% of patients treated with sorafenib and 19% of patients treated with sunitinib (Belum et al., 2013; Lacouture et al., 2008). Risk for these reactions with regorafenib may be even higher than with other drugs in this class. A meta-analysis of 500 patients with mCRC who were treated with regorafenib found that 60% developed hand-foot skin reaction (Belum et al., 2013).

Evidence supports a strategy of actively preventing dermatologic side effects, rather than waiting to begin treatment once they occur (Lacouture et al., 2010). Prevention of skin toxicities was studied in a phase 2 trial of panitumumab (Vectibix®), a monoclonal antibody that targets the epidermal growth factor receptor and is known to cause hand-foot skin reactions (Lacouture et al., 2010). Patients were randomly assigned to preemptive skin treatment or reactive skin treatment regimens. The preemptive regimen began one day before the administration of the first panitumumab dose. It entailed applying skin moisturizer to the face, hands, feet, neck, back, and chest each morning; using sunscreen before going outdoors; applying a topical steroid (1% hydrocortisone cream) to the face, hands, feet, neck, back, and chest at night; and using doxycycline 100 mg twice per day. In contrast, the reactive regimen (beginning after the development of skin reactions) included any treatments the investigator deemed necessary to manage skin toxicity and could be provided at any time during the study. Patients in the reactive skin care group were not prohibited from using skin moisturizer or sunscreen at other times if they chose to do so. In the study, the incidence of skin toxicities during the six-week skin treatment period was reduced by more than 50% in the preemptive skin care group compared with the reactive skin care group (Lacouture et al., 2010). In addition, patients in the preemptive skin care group reported less impaired quality of life than patients in the reactive skin care group.

Hypertension

Hypertension is a major clinical issue with antiangiogenic agents and is an independent risk factor for renal and cardiovascular events (Grenon, 2013; Maitland et al., 2010). A meta-analysis by Wang et al. (2014) found that 28% of patients with mCRC who are treated with regorafenib develop hypertension. This meta-analysis reported that the incidence of high-grade
**TABLE 1. Comparison of Hand-Foot Skin Reaction and Hand-Foot Syndrome**

<table>
<thead>
<tr>
<th>Clinical Entity</th>
<th>Presentation</th>
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<tbody>
<tr>
<td>Hand-foot skin reaction</td>
<td>Located on the ventral digit tips, over the interphalangeal joints, thenar and hypothenar in hands. Characterized by acral pain and dysesthesia. Located on the ventral surfaces of the feet, heels, and forefoot.</td>
</tr>
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Note. Based on information from Hagopiana & Packera, 2010; Son et al., 2009.

Hypertension ranged from 3%-36% (Wang et al., 2014). In comparison, the incidence of grade 3 or 4 hypertension in patients with CRC who were treated with another antiangiogenic agent, bevacizumab, was about 5%-18% (Genentech, Inc., 2012). Because of these issues, the Investigational Drug Steering Committee of the NCI convened an expert panel to study cardiovascular issues associated with therapies that target VEGF (Maitland et al., 2010). The panel recommended that (a) a formal risk assessment for potential cardiovascular complications should be conducted on all patients for whom these therapies are being considered; (b) preexisting hypertension should be identified and addressed before anti-VEGF therapy is started; (c) blood pressure should be actively assessed throughout treatment, with more frequent assessments during the first cycle of treatment; and (d) the blood pressure goal for most patients should be lower than 140/90 mmHg, or less than that for patients with preexisting cardiovascular risk factors (Maitland et al., 2010).

Treatment of hypertension in patients with cancer is guided by the same principles as hypertension treatment in other patient populations. However, hypertension should be approached aggressively in patients taking VEGF-targeted therapies, with referral to a specialist if response to antihypertensive maneuvers is not adequate (Maitland et al., 2010). Home blood pressure monitoring may aid early detection of hypertension (Eisen et al., 2012). Patients who are capable should be encouraged to use home blood pressure monitoring and should be instructed to contact the care team should the systolic or diastolic pressure values exceed the target range.

**Cardiac, Venous, and Arterial Toxicity**

Antiangiogenic therapies must be used with caution in patients with clinically significant cardiovascular disease or preexisting congestive heart failure (des Guetz, Uzzan, Chouahlia, & Morere, 2011). Systolic cardiac function should be assessed regularly through left ventricular ejection fraction (LVEF) measurement by echocardiography, magnetic resonance imaging, or multigated acquisition. Because LVEF alone is not an adequate early marker of cardiac damage, other ways to measure cardiac function during cancer treatment are currently being studied, such as the use of biomarkers and identification of subclinical changes in diastolic function (Eisen et al., 2012).

**Kidney and Liver Toxicity**

Prompt diagnosis and treatment of renal toxicity is vital in any patient receiving cancer therapy to reduce the risk of long-term complications, such as chronic kidney disease (Perazella, 2012). Older adult patients and those with preexisting renal problems may be at increased risk of renal toxicities induced by cancer treatment.

In its early stages of kidney disease, proteinuria has no signs or symptoms. In more serious cases, foamy urine may be seen, or swelling in the hands, feet, abdomen, or face (National Institute of Diabetes and Digestive and Kidney Diseases, 2009). Even mild proteinuria induced by anti-VEGF therapy may indicate serious renal damage (Izzedine, Soria, & Escudier, 2013). Treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers can decrease the urine protein levels, as well as decrease the risk of progressive renal disease (Armstrong, Wen, Gilbert, & Schiff, 2012).

Patients scheduled to be treated with an antiangiogenic drug should have a thorough assessment of liver function prior to and during therapy (Duong & Loh, 2006; Eisen et al., 2012). Liver function tests, such as bilirubin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase, should be part of the nursing plan (Duong & Loh, 2006). Severe hepatotoxicity leading to fatality has been reported in trials (ASISP, 2013; Grothey et al., 2013).

**Hemorrhage and Wound Healing**

Angiogenesis is a necessary part of wound healing. Therefore, antiangiogenic agents may impede wound healing by preventing the growth of new blood vessels, interfering with platelet-endothelial cell interaction, and decreasing VEGF-induced tissue factor on endothelial cells (Armstrong et al., 2012). Similarly, interference with angiogenesis can leave patients vulnerable to hemorrhage (Sanofi-Aventis, 2012). In particular, patients receiving ziv-aflibercept should be educated about and monitored for the signs and symptoms of bleeding (Sanofi-Aventis, 2012). To reduce the risk of serious hemorrhage, hypertension should be tightly controlled. Patients who need concomitant treatment with an anticoagulant should be closely monitored (Eisen et al., 2012).

**TABLE 2. Common Terminology Criteria for Adverse Events: Hand-Foot Skin Reactions and Syndrome**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis) without pain</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain that limit instrumental activities of daily living (ADLs) &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Severe skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain that limit self-care ADLs &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Examples of instrumental ADLs include preparing meals, shopping, and managing basic finances.

<sup>b</sup> Examples of self-care ADLs include bathing, dressing, feeding oneself, and using the toilet while not being bedridden.

Note. Based on information from National Cancer Institute, 2010.
Normal, Grade 1: Non-Urgent
Prevention, support, teaching, and follow-up care as required

Patient care and assessment
Nurse assessment:
- Screen for skin changes at first visit; re-assess at each visit and at peak times for onset.
- The only known cure for PPE related to chemotherapy is dose reduction or interruption.
- The timing of onset, appearance, distribution, and skin changes vary with each treatment cycle.

Patient self-assessment:
- Assess skin daily. Notify oncologist at next scheduled visit or earlier if symptoms worsen.
- Assess for early signs of PPE, including
  - Tingling and/or numbness (often first sign)
  - Dry, furrowed skin that becomes reddened or darker (in non-Caucasian patients)
  - Painless swelling or tenderness on the palms of the hands, pads of the fingers, soles of the feet and behind the knees, groin, axilla, and below the breast.

Skin care and hygiene
- Clean hands, feet, and skin fold areas with lukewarm water; gently pat dry.
- Wash sweat from skin.
- Avoid hot water (e.g., while bathing, cleaning dishes).
- Apply emollient creams or lotions with lanolin to keep skin hydrated; apply on intact skin—liberally, gently, and often.
- Use keratolytics (urea and salicylic acid) to remove overgrown skin.
- Avoid sun exposure during treatment. Use sun block.
- Avoid tight-fitting clothes, shoes, socks, belts, and jewelry, as well as harsh fabrics.
- Do not apply tight bandages, dressings, or adhesive tape to skin.

Avoid constrictive and mechanical stress.
- Do not immerse hands in strong detergent, bleach, or other chemicals. Use non-rubberized protective gloves.
- Do not use hands for activities that might cause abrasion or mechanical stress (e.g., clapping, typing), require tight gripping (e.g., tools, musical instruments, driving), and vigorous activities (e.g., jogging, aerobics).
- Avoid leaning on bony prominences (e.g., elbows, knees).
  - Sit or lie on padded surfaces.
  - Raise legs with cushions when possible.
  - Place pillow between knees or wear pajamas if rubbing of legs occurs during sleep.

Regulate temperature.
- Use gel shoe inserts for cushioning and reducing friction.
- Avoid situations that raise body temperature (e.g., steam saunas, hot baths, heating pads, vigorous exercise).
- Do not wear rubber gloves for dishwashing because they intensify heat.

Dietary management
- Promote adequate hydration and nutrition during treatment to help prevent skin dryness or desquamation.
- Recommend daily fluid intake of 8–12 cups (unless contraindicated) to help keep skin intact.
- Promote a well-balanced diet high in protein and vitamins B and C.

Pharmacologic management
- Advise patients to avoid using topical anesthetics or diphenhydramine-containing creams during treatment because these may exacerbate skin toxicity.

Patient education and follow-up
- Reinforce when to seek immediate medical attention.
  - Temperature greater than or equal to 38°C and/or presence of redness, discharge or odor from any open areas; possible infection
  - Unable to perform ADL; reflects deteriorating patient status and severity of PPE
  - Uncontrolled pain in hands, feet, and intertriginous areas
- Instruct patient or family to call back if symptoms worsen or do not improve.
- If indicated, arrange for nurse-initiated telephone follow-up or physician follow-up for additional assessment.

Grade 2: Urgent
Requires medical attention within 24 hours

Patient care and assessment
- Collaborate with physician as required.
  - Treatment delays, reductions, or discontinuation of treatment; new or change in prescriptions (analgesics, antibiotics, corticosteroids)
  - Laboratory and diagnostic tests: CBC and blood cultures if infection suspected
- Arrange for additional evaluation and assessment in an ambulatory setting.
- Arrange for specific skin care and dressings as necessary.

Management of skin complications
Pain
- Anticipate need for pain management: systemic or topical analgesics and/or topical steroids
- Cool packs on palms of hands or soles of feet may alleviate pain. Alternate on and off for 15–20 minutes at a time.

Local infection
- Review laboratory tests, culture any suspicious areas, and assess temperature.
- Review prescribed medications with patient and consider antibiotic treatment and/or topical steroids.

(Continued on the next page)

FIGURE 4. Algorithm for Managing Hand-Foot Syndrome or Hand-Foot Skin Reaction
Gastrointestinal Perforation or Fistula Formation

Prior to treatment with regorafenib or ziv-aflibercept, patients should be assessed to identify those at high risk for gastrointestinal perforation (Eisen et al., 2012). The assessment should include inquiring about a history of diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy or colonoscopy, resection of the primary tumor, gastrointestinal obstruction, and previous surgeries. Targeted agents for mCRC are commonly associated with gastrointestinal AEs, and monitoring for signs such as fever, abdominal pain, constipation, and vomiting is necessary but may not be sufficient (Eisen et al., 2012). A case series of gastrointestinal perforation in patients treated with bevacizumab found that, although patients displayed these common symptoms of gastrointestinal AEs as well as leukocytosis, it was uncommon for patients to present with tachycardia, hypotension, or sepsis (Badgwell et al., 2008). Fistulas may be clinically silent, but they may be detected with surveillance imaging (Thornton et al., 2012). However, gastrointestinal perforation is rare and no specific guidelines exist for surveillance beyond the normal surveillance for colon cancer.

Because management of patients receiving antiangiogenic agents can be complicated by poor wound healing, antiangiogenic therapies are not recommended within 28 days before or 28 days after surgery. Nonsurgical interventions, including a percutaneous intra-abdominal catheter, bowel rest, and IV antibiotics, may be feasible alternative options and should be considered (Badgwell et al., 2008).

Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) is a neurologic toxicity sometimes seen with VEGF-targeted therapies (Armstrong et al., 2012). The clinical manifestations, which often have an acute onset, include headaches, seizures, confusion, and occasional cortical blindness (Armstrong et al., 2012). The syndrome can be diagnosed using MRI (Chelis et al., 2012). RPLS usually resolves quickly with treatment of hypertension and cessation of anti-VEGF therapy, with a complete recovery in the majority of cases (Armstrong et al., 2012; Chelis et al., 2012).

Fatigue

Cancer-related fatigue is distressing, persistent, and generally diminishes the patient’s quality of life (NCCN, 2013). Fatigue is a common side effect of regorafenib and ziv-aflibercept (ASHSP, 2013; Grenon, 2013; Sanofi-Aventis, 2012). Patients should be assessed for fatigue prior to beginning treatment and monitored for the emergence or exacerbation of fatigue during treatment. This should include a review of disease status and treatment status to determine whether disease recurrence or progression may be contributing to the fatigue. All medications and supplements should be reviewed to identify potential causes of fatigue and sedation. The onset, pattern, and duration of fatigue should be explored (Eisen et al., 2012; NCCN, 2013). Any underlying factors should...
be promptly treated. In addition, teaching patients about ways in which they can cope with fatigue can encourage them to continue therapy. Patients should be counseled to conserve energy, to reschedule activities for periods of peak energy, and to stay active to improve sleep patterns. Stress management and relaxation techniques may be helpful for some patients (Eisen et al., 2012).

Conclusion

The antiangiogenic agents regorafenib and ziv-aflibercept are important additions to the treatment of mCRC. However, similar to other therapies in the antiangiogenic class, these new agents are associated with numerous and potentially serious AEs. Nurses play a crucial role in maximizing the benefits that patients may derive from these agents by creating and implementing nursing care plans—that include patient education about side effects and self-management—and routinely assessing patients for side effects of treatment. Prompt treatment of any AEs will promote effective treatment with these agents.

Editor’s note: Ramucirumab (Cyramza®) was approved by the U.S. Food and Drug Administration on July 15, 2015, for use in combination with FOLFIRI (folinic acid [leucovorin], 5-fluorouracil [Adrucil®], and irinotecan [Camptosar®]) for the treatment of patients with mCRC. For more information, visit www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm444496.htm.

References


Implications for Practice

- Increase detection of early symptoms of adverse effects of regorafenib (Stivarga®) and ziv-aflibercept (Zaltrap®).
- Be knowledgeable about and able to identify and manage skin toxicities resulting from the use of regorafenib and ziv-aflibercept.
- Enhance patient adherence to the regorafenib and ziv-aflibercept therapies by providing practical clinical tools.


