

Improving Outcomes for Patients With Metastatic Colorectal Cancer: Challenges and Strategies

PRESENTED BY LESLIE A. SWANSON,¹ ARNP, and KATHLEEN BOYLE,² PA-C

From ¹University of Washington/Seattle Cancer Care Alliance; ²Dana-Farber Cancer Institute, Boston, Massachusetts

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Abstract

At JADPRO Live 2019, Leslie A. Swanson, ARNP, and Kathleen Boyle, PA-C, reviewed guideline-concordant molecular testing and therapy in patients with metastatic colorectal cancer (mCRC), the clinical significance of emerging data for existing and novel agents used to treat mCRC, and the management of adverse events associated with mCRC therapies.

While colorectal cancer remains one of the most commonly diagnosed malignancies over the past 30 years, outcomes have improved due to increased screening, the approval of new cytotoxic and targeted drugs, and the integration of multiple different treatment regimens in patients, as described at JADPRO Live 2019 by Leslie A. Swanson, ARNP, nurse practitioner at the University of Washington/Seattle Cancer Care Alliance, and Kathleen Boyle, PA-C, physician assistant at Dana-Farber Cancer Institute.

Effective treatments, however, often pose side effects, the management of which usually falls upon advanced practitioners. Ms. Swanson and Ms. Boyle devoted much of the session to advising clinicians of these supportive care issues.

COLORECTAL CANCER POPULATION

In the United States, nearly 150,000 cases of colorectal cancer (CRC) were diagnosed in 2019, with deaths estimated at more than 50,000 (Siegel, Miller, & Jemal, 2019). While more than 90% of cases occur in adults age 50 and older (with age being the primary risk factor), the incidence of CRC is increasing in younger adults, with a 2% increase in individuals diagnosed under the age of 50 between 1992 and 2013. The reason for this trend remains unclear, according to Ms. Swanson. As a result of this trend, in 2018, the American Cancer Society lowered the recommended age for CRC screening to 45.

“It’s important to note that this rising trend is seen in our unscreened population. These are individuals that we’re relying on our colleagues in primary care to identify and refer

to us,” Ms. Swanson said. “We’re also relying on our patients who are young to seek medical attention for symptoms.”

While screen-detected cancers are often caught early and cured, approximately 71% of young-onset colorectal cancer is diagnosed at stage 3 or 4, possibly due to a lack of screening and delays in recognition.

STANDARD TREATMENT

The standard algorithm from the National Comprehensive Cancer Network (NCCN) Guidelines considers primary treatment for CRC based on stage. For metastatic disease, multiple factors help determine the sequencing of therapies: patients’ previous therapies, the biology of their tumor, patient characteristics and comorbidities, goals of treatment, and side effects of treatments. “Deciding on treatment sequence can be challenging for clinicians,” Ms. Swanson added.

FOLFOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin) and FOLFIRI (5-FU, leucovorin, irinotecan) are standard-of-care regimens and are commonly combined with anti-VEGF therapy (bevacizumab). No specific biomarkers are required for these drugs, but the sequence of therapy is typically bevacizumab in the first and second line, aflibercept or ramucirumab in the second line, and regorafenib in the third line and beyond.

Some patients may be appropriate for more intensive therapy with the triplet FOLFOXIRI or FOLFIRINOX (5-FU, leucovorin, oxaliplatin, irinotecan). “Triplet therapy has been shown to increase response rate and improve progression-free survival; however, it comes with increased toxicity and can make the approach to second-line treatment difficult,” Ms. Swanson added. These regimens are best reserved for patients with excellent performance status, those desiring aggressive care (for example, maybe young-onset patients), and patients who need significant downstaging.

After a very good response to first-line treatment, clinicians often opt to de-escalate the dose or switch to a simpler maintenance regimen in an attempt to maintain response to treatment and reduce toxicity. Studies suggest these approaches do not compromise outcomes.

PRECISION MEDICINE ENTERS THE ALGORITHM

Molecular profiling of tumors has greatly altered the approach to treatment, allowing clinicians to individualize CRC treatment. At Dana Farber, clinicians typically start patients on FOLFOX while waiting for OncoPanel results. “That’s really when we start perusing the lists of clinical trials,” said Ms. Boyle. “We stick to the standard fluorouracil-based regimens but keep a constant eye on new therapies.”

In CRC, the most important signaling pathways are RAS, RAF, MEK, ERK, and MAPK. *RAS* mutations are abundant in many types of cancer, including 45% of CRC tumors. Numerous studies have shown that response to EGFR inhibitors (cetuximab and panitumumab) are limited to patients lacking *RAS* mutations. Therefore, patients with metastatic CRC who are both *RAS* wild type and *BRAF* wild type are usually considered for treatment with cetuximab and panitumumab, in addition to standard chemotherapy.

The landmark CALGB/SWOG 80405 trial evaluated whether in *KRAS* wild-type patients, cetuximab or bevacizumab was the better partner to chemotherapy (Venook et al., 2017). The study found no overall survival difference between the arms, with median survival approaching 30 months and median progression-free survival approximately 10 months with either regimen. But interestingly, differences did emerge based on the location of the tumor, with longer survival for patients with left-sided disease (Venook et al., 2016). “This could be further broken down based on which drug was given,” Ms. Boyle noted. “Patients with left-sided primary tumors responded better to cetuximab plus chemotherapy than they did with bevacizumab plus chemotherapy; right-sided tumors had improved survival with bevacizumab, vs. cetuximab... It’s necessary for us to think about the sidedness of our patients’ tumors.”

Patients who are *KRAS* wild type but *BRAF*-mutated are considered for a *BRAF* inhibitor plus MEK inhibitor (i.e., dabrafenib/trametinib, vemurafenib/irinotecan, and encorafenib/binimetinib). For patients with HER2-amplified tumors, clinicians can consider adding trastuzumab, pertuzumab, and lapatinib (or in a clinical trial, tucatinib). In addition, microsatellite insta-

bility is important. Patients who are microsatellite instability-high (MSI-H) are candidates for immunotherapy with pembrolizumab, nivolumab, and ipilimumab, Ms. Boyle said.

Speakers expanded on the topic of *BRAF*-mutated disease, noting that these tumors are associated with aggressive biology, limited response to chemotherapy and EGFR antibodies, and short survival time, but targeted treatment can improve outcomes, as shown in the phase II SWOG S1406 study in which the addition of the *BRAF* inhibitor vemurafenib to cetuximab/irinotecan led to a 58% reduction in risk of progression (Kopetz et al., 2017).

Moreover, the phase III BEACON trial tested *BRAF*/MEK combination targeted therapy by comparing encorafenib and binimetinib plus cetuximab (triplet) to encorafenib/cetuximab (doublet) and to chemotherapy/cetuximab (Kopetz et al., 2019). In the recently updated survival analysis, median overall survival was 9.3 months with both the doublet and triplet, vs. 5.9 months with standard chemotherapy (Kopetz et al., 2020). Data from BEACON have been submitted for regulatory approval of the doublet—encorafenib/cetuximab—for the treatment of *BRAF*-mutated metastatic CRC. *BRAF* inhibitor-based treatment has recently been included in the NCCN Guidelines as well.

MANAGING TOXICITIES RELATED TO CHEMOTHERAPY

“Managing our patients comes down to making sure we’re providing good patient education, talking about common and uncommon side effects, and informing patients on how and when to notify the clinic,” said Ms. Swanson.

Toxicity with 5-FU depends on the duration of treatment and rate of administration. This is important when patients are receiving FOLFOX or FOLFIRI, which involves both a 5-FU loading dose and 46-hour infusion with a portable pump, Ms. Swanson said.

Common side effects include fatigue, nausea, vomiting, diarrhea, mucositis, and cytopenias; the leukopenia nadir is 9 to 14 days. Severe toxicity typically occurs in the first 96 hours. Uridine triacetate is an antidote that can palliate symptoms of 5-FU toxicity and allow earlier resumption of chemotherapy. “If we detect a DPD deficiency (DPD is an enzyme that breaks down fluorouracil),

we can also make dose modifications in 5-FU to help decrease the toxicity without impacting efficacy,” she said.

Common side effects of irinotecan include alopecia, diarrhea, abdominal pain, mucositis, cytopenias, and cholinergic syndrome (diaphoresis, flushing, and rhinitis). Acute diarrhea is dose-dependent and typically accompanied by other symptoms, including abdominal pain, rhinitis, and salivation. These symptoms typically respond rapidly to atropine, which can be integrated into the premedication. Delayed diarrhea occurs 24 hours after dosing, is noncumulative, and occurs at all dose levels. UGT1A1 genotyping can detect the presence of heterozygous or homozygous variations, which can then indicate a higher risk of severe irinotecan toxicity.

“Early detection leads to earlier intervention, so this involves talking about symptom management with your patients,” she said. For diarrhea that is refractory to loperamide, octreotide can be used at a starting dose of 100 to 150 µg subcutaneously three times a day, escalating as needed. Researchers are evaluating probiotics, budesonide, glutamine, octreotide LAR, and antibiotics for prophylaxis.

While waiting for the results of DPD and UGT1A1 testing, clinicians should remember that the 5-FU bolus can be modulated as a way of ameliorating the potential for 5-FU toxicity. Once test results are known, dose modifications can be made as necessary. The percentage of individuals with a genetic mutation impairing their metabolism of 5-FU and irinotecan is very small; therefore, routine screening for DPD and UGT1A1 deficiency is not standard.

The primary concern with oxaliplatin is acute and delayed peripheral neuropathy. Acute neuropathy can be exacerbated by cold temperatures; patients are often instructed to avoid eating, drinking, or touching things that are not room temperature or warmer for the first 3 to 7 days after infusion. Acute neuropathy typically resolves within 14 days, while delayed neuropathy presents more than 14 days post-infusion, is persistent, may interfere with activities of daily living, and can result in treatment discontinuation. Management for painful peripheral neuropathy includes dose reductions and the use of gabapentin, duloxetine,

and venlafaxine. The benefit of acupuncture is being studied.

A recent study evaluated the use of oral cryotherapy during oxaliplatin infusion and found it to be a tolerable and cost-effective method for diminishing oral thermal hyperalgesia (Bauman et al., 2019). This should be started with the first or second dose of oxaliplatin; it is not appropriate for patients who have been on oxaliplatin for a period of time.

Oxaliplatin is also associated with infusion reactions, typically occurring during cycle 6 or 7. For the patient who experiences symptoms such as rash, hives, sudden cough, stridor, swelling, or hypotension, laryngopharyngeal dysesthesia (although rare) should be ruled out. Patients often describe laryngopharyngeal dysesthesia as a feeling of choking or being unable to breathe. Management includes stopping the infusion, reassuring the patient, and encouraging relaxation—followed by restarting the medication. A true allergy requires stopping the infusion, treating with rescue medications, then resuming treatment at a slower rate after symptom resolution. Subsequent infusions should be accompanied by additional premedication and should be run over 4 to 8 hours.

MANAGING TOXICITIES RELATED TO BEVACIZUMAB AND PATHWAY INHIBITORS

With bevacizumab, serious adverse effects include gastrointestinal perforation, delayed or impaired wound healing, and hemorrhage, although the most common ones encountered in the clinic are proteinuria, thromboembolism, and hypertension. A urinalysis should be done at baseline and periodically during treatment; for a urinary protein > 2 gm, treatment is held until a 24-hour urine shows urine protein < 2 gm. Hypertension, which is dose-dependent, is another common side effect that if left untreated can produce cardiovascular complications. In most cases, early recognition, initiation of antihypertensives, and holding bevacizumab is sufficient, Ms. Swanson said.

EGFR inhibitors are associated with xerosis, pruritis, paronychia, and trichomegaly that leads to eye irritation. Acneiform rash, the first and most common cutaneous toxicity, occurs in 60% to 80% of patients, typically peaking within the first 2 to 3

weeks of treatment then tapering off. Xerosis and paronychia, on the other hand, occur later and build with intensity as treatment is continued. For acneiform rash, management is both prophylactic (with regular use of emollient creams) and reactive (initiation of low-dose tetracyclines, escalating to twice daily if needed). Other interventions include topical steroid creams, metronidazole or clindamycin cream, and antihistamines. Cutaneous side effects diminish in intensity with continued exposure. Patients should avoid hot baths and prolonged sun exposure, as heat can flare the intensity of the rash. “We should also be using our resources—reaching out as needed to our dermatology colleagues,” she said.

Similarly, emollient lotions should be used preemptively and throughout treatment to manage xerosis cutis, which occurs in approximately 35% of patients. Damaged skin is prone to infection; therefore, the use of soap substitutes containing microbial agents (such as chlorhexidine), can be helpful. Painful nail disorders like paronychia occur in 10% to 15% of people and can become infected by *Staphylococcus*, *Enterococcus*, and *Pseudomonas*. Broad-spectrum antibiotics can be indicated, with culture considered for nonresponders. To prevent mild paronychia from becoming infected, topical treatment with an antibiotic cream or daily soaks in saline solution can help.

Hand-foot syndrome has subtle differences from hand-foot skin reaction as seen with regorafenib and BRAF inhibitors. It can be managed with topical steroids (0.05% cortisol cream) and celecoxib 200 mg bid. If symptoms persist, consider dose interruptions and dose reductions to allow patients to continue on treatment, she advised.

Hand-foot skin reaction usually appears on the soles of the feet, with localized areas of skin trauma or friction that present as hyperkeratosis. Preventive measures are similar to those of hand-foot syndrome: patients should regularly apply emollient lotion with at least 10% urea; avoid hot water, fragrance, lotions, and excessive sun exposure; wear well-fitted shoes; and limit friction with cotton socks. Reactive treatment is with emollient lotion that includes 20% to 40% urea. Moisturizers containing salicylic acid, ammonium lactate, or alpha hydroxy acid, or cooling hand-foot baths containing magnesium sulfate, can soften hyperkeratosis.

Other potential side effects of anti-EGFR drugs include fatigue, weight loss, diarrhea, and electrolyte imbalances. Providers should monitor serum magnesium and potassium during and after treatment and replenish electrolytes as clinically indicated.

Common side effects of BRAF inhibitors include hypertension, fatigue, and skin reactions. Those related to MEK inhibitors are skin toxicities, diarrhea, elevations in liver enzymes, and decreased left ventricular ejection fraction. Anti-HER2 agents can be associated with fatigue, diarrhea, and decreased left ventricular ejection fraction. Patients on MEK inhibitors and anti-HER2 agents should have a MUGA or echocardiogram at baseline and every 3 months during treatment, according to Ms. Swanson.

EMERGING APPROACH: IMMUNOTHERAPY

Much excitement surrounds the potential for immunotherapy in metastatic CRC. To this end, pembrolizumab, nivolumab, and/or ipilimumab can be considered for patients with MSI-H or deficient mismatch repair (dMMR) tumors who progress after first-line chemotherapy. Support for this approach was built upon the results of the CheckMate 142 trial, in which 34% of patients responded to nivolumab and 62% achieved stable disease (Overman et al., 2017).

Immune-mediated toxicities can affect all organ systems. While only 5% of these are serious, up to 50% of patients will experience at least mild toxicity. Patients should be alert to any “new and sudden-onset” physical symptoms, Ms. Swanson said. Treatment of immune-related toxicities is guided by the grading system:

- Grade 1: Continue immunotherapy under close monitoring, with the exception of side effects that are neurologic, hematologic, or cardiogenic.
- Grade 2: Hold the immunotherapy and consider resuming when the symptoms are grade 1 or less; corticosteroids can be considered.
- Grade 3: Hold the immunotherapy and initiate steroids, starting with prednisone 1–2 mg/kg/day, or methylprednisolone 1–2 mg/kg/day.

- Taper steroids slowly over 4 to 6 weeks; if symptoms do not improve within 48 hours, consider infliximab to prevent the activity of endogenous tumor necrosis factor alpha.

Patients starting on immunotherapy should get a complete blood count, a comprehensive metabolic panel, and thyroid-stimulating hormone (TSH) and T4 tests. As patients continue therapy, additional testing is warranted for areas of concern. “Symptoms can become quite severe very quickly for the patient who is on immunotherapy,” Ms. Boyle noted.

PUTTING IT ALL TOGETHER

Concluding the session, Ms. Swanson outlined the general approach to sequencing treatments. In the first-line setting, a doublet or triplet (FOLFOX, FOLFIRI, FOLFOXIRI) plus or minus bevacizumab is indicated for patients who can manage intensive therapy. For RAS wild-type patients, cetuximab or panitumumab is added. Subsequent therapies can involve targeted agents, or oral agents such as regorafenib and trifluridine plus tipiracil. For MSI-H patients, nivolumab plus or minus ipilimumab, or single-agent pembrolizumab are indicated.

“We should conduct guideline-concordant molecular testing in patients with metastatic CRC,” Ms. Boyle added. “We should select guideline-concordant therapy but we also always need to evaluate the potential clinical significance of emerging data for existing and novel agents. And we need to stay on top of the data for managing adverse events associated with these treatments.” ●

Disclosure

Ms. Swanson and Ms. Boyle have no conflicts of interest to disclose.

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