Optimizing the Care of Patients With Colorectal Cancer in Clinical Practice

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Abstract

At JADPRO Live 2023, presenters emphasized the importance of increasing colorectal cancer screening in high-risk groups, reviewed guidelines in the adjuvant and metastatic setting, and outlined clinical and molecular profiles to consider when discussing and determining treatment options with patients.

Colorectal cancer is the third most common cancer diagnosis in men and women, and the second leading cause of cancer-related deaths. At JADPRO Live, Mary B. Morgan, MSN, ANP-BC, AOCN®, of Simmons Comprehensive Cancer Center, and Tammy Triglianos, DNP, ANP-BC, AOCNP®, of UNC Lineberger Comprehensive Cancer Center, explored screening recommendations, the latest treatments, and the role of biomarker testing in colorectal cancer.

SCREENING

The highest incidence of colorectal cancer is in patients between the ages of 65 to 74, with the median age of onset around 66. This age has shifted since the early 2000s, when the median age of onset was 72. This approximately 2% increase in incidence in younger patients has been documented in recent years. Table 1 describes 5-year survival data based on the stage of disease.

The incidence of colorectal cancer remains higher among Black people than any other racial or ethnic group, at 20% higher than non-Hispanic White people. Mortality rates are also about 40% higher in the Black population than in the non-Hispanic White population.

"These are important statistics to keep in mind when we think about screening rates and strategies to increase screening, especially in light of these health disparities," noted Dr. Triglianos.

Approximately 30% of the US population is not up to date on screening. Current colorectal screening guidelines consist of a physical exam, history, and colonoscopy. Colonoscopy can locate and remove polyps, which can prevent colon cancer or detect cancer at an earlier stage. Screening should begin at age 45 for most people. It should

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be considered for those under 45 if there is a family history of colorectal cancer or polyps, if symptoms are present, or in higher-risk groups such as Black and Hispanic populations.

Barriers to screening include the provider not recommending screening, fear or worry about the procedure or outcome, financial burden, and medical mistrust. Strategies to address these include local involvement to engage communities about screening, developing a screening policy and measuring progress, and being persistent with reminders to get screened.

BIOMARKER TESTING

Key principles of the treatment of colorectal cancer include clinical parameters such as the burden of metastatic disease, potential for curative resection, age, performance status, and comorbidities. Tumor and molecular parameters include a patient's *KRAS* mutation and microsatellite status, the sidedness of a tumor, and identifying molecular markers of the cancer with next-generation sequencing.

Biomarker testing identifies genes, proteins, and other substances to provide information about the cancer. Circulating tumor DNA, sometimes referred to as a liquid biopsy, is a highly specific cancer biomarker. It can measure minimal residual disease, which may be used to more accurately monitor tumor burden levels, as well as the effectiveness of a treatment or for cancer recurrence. While it has become useful in cancer management, further information is needed to define its use in the clinical setting.

ADJUVANT SETTING

Colon Cancer

Adjuvant chemotherapy for stage III disease is aimed at eradicating micrometastatic disease and thereby prevent cancer recurrence and cancer-related mortality. Generally, chemotherapy is given within 4 to 8 weeks after surgery.

The MOSAIC trial confirmed improved disease-free and overall survival for patients with stage III colorectal cancer receiving 6 months of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared with fluorouracil and leucovorin. There was no benefit seen with FOLFOX in stage II disease, except in patients with high-risk disease. Adverse features associated with high-risk recurrence include a T4 lesion obstruction or perforation at diagnosis, a low number of sampled nodes, high-grade disease, lymphovascular invasion, and perineural invasion.

Studies have shown that there is no benefit in terms of disease-free survival or overall survival of adding oxaliplatin to fluoropyrimidines (such as capecitabine) in the adjuvant setting in older patients; the benefit has been restricted to patients under the age of 70 (McCleary et al., 2013).

"It's difficult to predict which subset of the elderly population would benefit," commented Dr. Triglianos. "Along with the risk of associated toxicities, such as neurotoxicity, these regimens should be evaluated and reserved for robust patients with a longer life expectancy."

Historically, adjuvant therapy has been administered as a 6-month course in colon cancer. However, there is substantial toxicity with oxaliplatin-based therapy, sometimes resulting in permanent neurotoxicity. The IDEA trial evaluated the duration of treatment through a prospective pooled analysis of six phase III trials. Results in stage III colon cancer did not demonstrate the noninferiority of 3 vs. 6 months of adjuvant FOLFOX or capecitabine plus oxaliplatin (CAPOX). However, the difference in survival was marginal, and for those who received CAPOX, 3 months of therapy was as effective as 6 months. In addition,

Table 1. Treatment by Stage

Cancer Stage	Treatment	5-yr relative survival rate
Stage I (localized)	Surgery	91%
Stage II (localized)	Surgery	91%
Stage III (regional)	Surgery + chemotherapy	73%
Stage IV (distant)	Chemotherapy + targeted therapy +/– surgery	16%

Note. National Cancer Institute Cancer Stat Facts: Colorectal Cancer.

there was a 1% difference in 5-year overall survival for 3 vs. 6 months of therapy (André et al., 2018). Data continue to support the use of 3 months of adjuvant treatment for most stage III disease.

"A risk-based approach and conversation with patients is necessary in determining the duration of adjuvant therapy," said Dr. Triglianos.

Rectal Cancer

Surgery is the mainstay of treatment for rectal cancer. However, clinicians must address the risk of microscopic residual disease in the pelvis as well as distant metastasis. There are two surgical approaches based on tumor location: lower anterior resection (LAR), which is sphincter sparing with no ostomy, and abdominoperineal resection (APR), which results in permanent ostomy. Wide surgical margins are often difficult to achieve, and therefore neoadjuvant treatment is used to decrease the risk of local and distant recurrence.

Total neoadjuvant treatment is a combination of chemotherapy and radiotherapy before surgical resection that has increased the rates of both clinical and pathological complete response, resulting in excellent long-term oncological outcomes compared with adjuvant chemoradiation therapy. National Comprehensive Cancer Network (NCCN) Guidelines recommend all patients who receive neoadjuvant chemoradiation should receive 3 to 4 months of adjuvant fluorouracil-based chemotherapy to decrease the risk of recurrence.

Since total neoadjuvant treatment was introduced, non-operative management of LARC patients with a clinical complete response after neoadjuvant therapy has gained acceptance as a potential treatment option in select cases. It is based on replacing surgical resection with safe and active surveillance in selected cases. Long-course radiation with capecitabine is recommended.

METASTATIC SETTING

The regimens of leucovorin, fluorouracil, and irinotecan (FOLFIRI) and FOLFOX have demonstrated prolonged survival with similar efficacy. The decision between either regimen should be based on toxicity and decision regarding a possible resection.

Concerning triplet vs. doublet therapy, TRIBE trial data showed improved outcomes when comparing FOLFOXIRI to FOLFOX or FOLFIRI, but this may not be an appropriate regimen for all patients. For the frailer patient or a patient with a lower burden of disease, it may be more reasonable to start with a doublet.

Adding targeted therapies has been shown to improve progression-free survival and overall survival benefits. Options include the antiangiogenic agent bevacizumab and EGFR inhibitors panitumumab or cetuximab, which are used in *KRAS* wild-type colorectal cancer.

Comorbidities also play a role in choosing between therapies. Bevacizumab is contraindicated for reasons such as uncontrolled hypertension, if the patient has had major surgery or injury 28 days before, or if the patient develops untreated brain metastases 4 to 6 weeks after. EGFR inhibitors are also associated with a significant rash in up to 50% to 100% of patients.

Tumor sidedness is another consideration. Right-sided tumors have had a better response to anti-VEGF treatment in the first-line setting, while left-sided tumors have had a better response to EGFR inhibitors in the first-line setting.

In the third-line setting and further, which is considered refractory disease, there are a few options. The standard of care per the NCCN Guidelines is regorafenib or trifluridine/tipiracil with or without bevacizumab. In the SUNLIGHT trial, trifluridine/tipiracil with bevacizumab showed clinically meaningful improvement in overall survival and progression-free survival when compared with trifluridine/tipiracil alone. Bevacizumab is given intravenously every 2 weeks, and the oral portion is given for 10 days out of 28, and not consecutively.

As it is dosed orally and intravenously, this requires educating the patient to help keep them on schedule. Having the assistance of a clinical pharmacist or a nurse navigator and preparing a calendar for the patient is integral. In addition, clinicians should address the potential side effects, such as neutropenia, anemia, fatigue, and diarrhea. Patients may require dose reductions or delays with this regimen.

In addition, fruquintinib was approved in November 2023 in the refractory setting.

Discussing best supportive care is also an option, as well as clinical trials either through one's

institution or an academic or NCI-designated cancer center.

"Hopefully, throughout your patient's treatment journey, you've been discussing goals of care with patients and their family and establishing a rapport, so that you as the advanced practitioner can have this difficult conversation with them," said Ms. Morgan.

MSI-H COLORECTAL CANCER

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors have an accumulation of errors in genetic sequences that are normally repeated, called microsatellites. Microsatellite instability means the genes that regulate DNA do not work correctly.

An MSI-high biomarker is a prognostic indicator. Patients with an MSI-high tumor tend to have a better prognosis than those patients with a microsatellite stable tumor. MSI-high can also be a predictive biomarker. These tumors tend to not respond as well to single-agent fluorouracil-based chemotherapy and can predict a positive response to immunotherapy. Without high-risk features, there is a favorable prognosis.

HER2 AMPLIFICATION

HER2 amplification, also known as *ERBB2*, is a nonhereditary marker. The frequency is fairly low, at 3% to 5%. As a prognostic biomarker, it can confer a poorer prognosis in breast and gastric cancer; however, its significance in colorectal cancer is unclear. As a predictive biomarker, it can predict less benefit derived from anti-EGFR agents and a potential to respond to anti-HER2 therapy (trastuzumab + pertuzumab, lapatinib, or tucatinib; or trastuzumab deruxtecan).

The MOUNTAINEER phase II trial evaluated the activity of tucatinib plus trastuzumab in patients with chemotherapy-refractory, *HER2*-positive, *RAS* wild-type unresectable or metastatic colorectal cancer who were previously treated with at least two lines of therapy. The results showed a median progression-free survival of 8.2 months and a median overall survival of 24.1 months. It is an oral and IV combination dosed twice a day and has been shown to be fairly well tolerated.

"The most common side effects I see in my practice are hepatotoxicity and diarrhea. Be sure to monitor the kidney and liver function of your patients," commented Dr. Triglianos.

BRAF

BRAF is a somatic mutation present in approximately 8% to 12% of colorectal cancers. It can be a prognostic indicator for overall survival and tends to have a poorer prognosis and poorer responses to standard therapy. *BRAF*-mutated colorectal cancer tends to be more common in females or right-sided tumors. These types of tumors behave more aggressively, indicating a need for a more aggressive treatment regimen. The mortality risk for patients with a *BRAF* mutation is more than two times higher than for those with a normal *BRAF* gene. It is also a predictive biomarker, indicating that *BRAF*-mutated tumors are unlikely to respond to EGFR inhibitors when given alone or in combination with chemotherapy.

The phase III BEACON clinical trial confirmed that the combination of encorafenib (a BRAF inhibitor), cetuximab (an EGFR inhibitor), and binimetinib (a MEK1/2 inhibitor) resulted in significantly longer overall survival and a higher response rate than standard therapy in patients with metastatic colorectal cancer with the *BRAF* V600E mutation after at least one line of systemic therapy. ●

Disclosure

Mary B. Morgan has no relevant financial relationships to disclose. Tammy Triglianos has served on the advisory board for Pfizer.

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