EXPERT PERSPECTIVES: THE NEXT ERA IN THE MANAGEMENT OF METASTATIC COLORECTAL CANCER

Background and scope for management of metastatic colorectal cancer

Colorectal cancer (CRC) can develop on either the left or right side of the colon or in the rectum. While CRC screening is recommended for the general population at age 45 years, there is a rising incidence of CRCs occurring in younger patients. A low index of suspicion is necessary for patients who present with suggestive symptoms. More distal colon or rectal cancers are more likely to present with changes in bowel habits and rectal bleeding, whereas more proximal tumors may have more nonspecific symptoms, such as fatigue and abdominal pain.[1,2] Treatment involves surgery, systemic therapy, and possibly radiation therapy, depending on the cancer's stage, characteristics, and location.[1,3,4]

Metastatic colorectal cancer (mCRC) is a common and deadly malignancy, responsible for an estimated 53,000 deaths in the United States in 2023 and a 5-year survival rate of only 14%.[5] Chemotherapy remains the initial treatment of choice.[5,6,7] Cytotoxic chemotherapy regimens, usually with a fluorouracil-based regimen, remain the preferred category 1 recommendation in the National

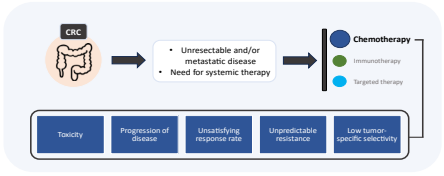

Figure 1

Comprehensive Cancer Network (NCCN) guidelines.[8] Cytotoxic chemotherapy offers an estimated median overall survival (OS) of 27 months.[9] Upon progression, OS drops to an estimated 6 months with second line-therapy. Targeted therapies represent a promising new approach to address the unmet needs to enhance the quality of life and treatment outcomes for patients with mCRC. These targeted therapies are increasingly being integrated into treatment due to their ability to extend OS and improve quality of life in select subgroups of mCRC patients.

Molecular profiling and tumor markers

The pathogenesis of CRC depends on its anatomical site within the colon, particularly distinguishing between the right and left sides. Right-sided tumors more often exhibit mutations in the DNA mismatch repair (MMR) pathway. Conversely, left-sided tumors often feature mutations in pathways like KRAS, APC, PIK3CA, and p53, with a polyp-like morphology.[1] Prognostically, left-sided tumors generally fare better overall, particularly in advanced stages, benefiting from chemotherapy and EGFR-targeted therapies.[1,2,3] In contrast, right-sided tumors typically show poorer response to standard regimens.[4] Thus, effective treatment planning and patient stratification depends on discerning the tumor's primary location—left or right side—and also the unique molecular profile. Molecular profiling is less relevant to localized CRC compared to advanced stages, where precision medicine has a direct impact on treatment decisions. MSI status is important for patients with localized CRC as it helps stratify patients into different prognostic and therapeutic groups.

The management of patients with mCRC has traditionally been limited to systemic cytotoxic chemotherapy.[8] In more recent years, the focus on precision medicine has allowed providers to tailor therapy based on identifiable targetable mutations.

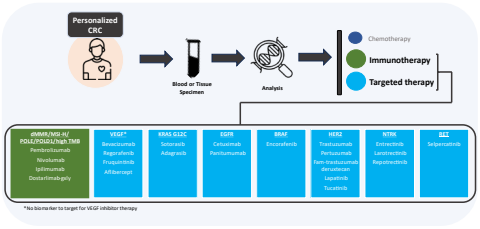

Figure 2

Targetable mutations such as KRAS, NRAS, BRAF, HER2 (ERBB2), and microsatellite instability (MSI)/MMR status are pivotal in guiding mCRC treatment decisions. Agents directed at these targets are useful for the treatment of mCRC as first- and subsequent-line treatment options and/or for certain circumstances when the patient has the potential targeted mutation. KRAS and BRAF mutations are frequently encountered in patients with mCRC, whereas mutations in RET, NTRK, and HER2 are less commonly observed. Testing of tumor gene status for KRAS/NRAS and BRAF mutations, HER2 amplifications and MSI/MMR status is recommended at diagnosis using tissue and/or liquid biopsy.[8] Testing may be carried out for individual genes or as part of a panel, with next generation sequencing (NGS) providing a comprehensive picture of the metastatic disease and an informative view for what treatment to choose.[10,11] NGS panels can pick up other actionable genetic alterations, such as NTRK and RET fusions, and may be carried out using either tissue or liquid biopsy.[11] Liquid biopsies offer a noninvasive alternative when tissue samples are inaccessible, providing quicker results with a potential for fewer procedural risks.[10,11] A limitation of liquid biopsy techniques is their tendency to overestimate tumor mutational burden (TMB), as it may capture genetic material from both cancerous and noncancerous cells. Repeat molecular testing postcytotoxic therapy is not required as changes in the key targetable molecular changes are rarely observed. Conversely, development of detectable resistance mutations may be observed after targeted therapy, warranting periodic reassessment for future targeted therapy decisions, such as if deciding to re-

expose a patient to a prior targeted therapy if decay of the resistance clone is observed.[8]

Precision medicine testing for all patients with CRC should start at a minimum with MMR or MSI, to determine immunotherapy response, prognostic insights, and Lynch syndrome screening.[8] Whether germline or somatic, mutations in the MMR genes (*MLH1, MSH2, MSH6, PMS2, EpCAM*) and somatic mutations in *POLE/POLD1* predict response to checkpoint inhibitor therapy.[8,12,13] This is of key importance as multiple first-line trials note improved short- and long-term survival from immunotherapy in patients with MSI CRCs as compared to chemotherapy. If a tumor is determined to be both MSI-H/dMMR and BRAF V600E, first-line therapy with a checkpoint inhibitor would generally be preferred, and a BRAF inhibitor regimen could be reserved for a later line of therapy.[8]

Treatment

5-Fluorouracil remains the cornerstone for the treatment of patients with mCRC. It is often combined with other agents such as oxaliplatin or irinotecan to enhance its efficacy. These regimens have demonstrated improvements in median OS and progression-free survival (PFS) and are considered first-line category 1 options in combination with targeted therapies or alone, depending on patient and disease characteristics.[8] FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) and FOLFIRI (5-fluorouracil, leucovorin, irinotecan) regimens have demonstrated comparable efficacy in terms of OS and PFS when used as first-line treatments in mCRC; median PFS is 9 to 12 months. FOLFIRINOX is also an option, combining all 3 agents (5-fluorouracil, oxaliplatin, irinotecan). Safety concerns with the use of these regimens include the potential for neurotoxicity, diarrhea, nausea, vomiting, and myelosuppression.[8,14,15] Targeted therapy may be added to the chemotherapy agents, or used alone, depending on the specific molecular alteration.

VEGF

In mCRC, VEGF is a therapeutic target. Therapies targeting VEGF such as bevacizumab, aflibercept, ramucirumab, regorafenib, and fruquintinib, are integral components of treatment strategies in mCRC to inhibit tumor growth and improve patient outcomes.[8] The 5-fluorouracil-based regimens in the first-line setting are commonly used in combination with the anti-VEGF agent bevacizumab, further optimizing efficacy outcomes in patients with mCRC.[8,16] Regorafenib, a small-molecule inhibitor of various kinases, may be used after progression on all standard chemotherapy.[8] Based on the CORRECT trial, use of regorafenib was associated with a median OS of 6.4 months, but with a PFS that was only 0.2 months longer than placebo.[17] Fruquintinib, another VEGF inhibitor, demonstrated a median OS of 7.4 months in the FRESCO-2 trial.[18] OS was 9.3 months for patients who had not received prior anti-VEGF inhibitor therapy.[19] Fruquintinib may be used as a treatment option for patients with mCRC who have progressed through all other available regimens before or after regorafenib.[8,18,19] VEGF inhibitors may cause toxicities including hypertension, proteinuria, bleeding, thromboembolism, and hand-foot syndrome.[8,17,18]

EGFR Mutations

The 5-fluorouracil-based regimens in the first-line setting are commonly used in combination with targeted anti-EGFR agents depending on the molecular profile of the tumor and tumor location, further optimizing efficacy outcomes in selected patients with mCRC. Anti-EGFR antibodies (cetuximab, panitumumab) are indicated for RAS wild-type left-sided tumors.[8] Both cetuximab and panitumumab, when combined with FOLFOX or FOLFIRI, have demonstrated improved response rates and PFS in first-line treatment of mCRC, particularly in patients with KRAS wild-type tumors.[20-22] Patients treated with EGFR inhibitors may experience skin rashes, diarrhea, electrolyte imbalances, and infusion reactions, requiring careful monitoring and supportive care management.[8,20-22] Studies, including the 80405 trial, have suggested that patients with left-sided colon cancers may derive more benefit from EGFR inhibitors compared to those with right-sided tumors.[8,23] These findings highlight the biological and molecular differences between left-sided and right-sided CRCs, influencing the patient's response to treatment. However, it is important to note that the PARADIGM study did not conclusively establish the superiority of left-sided treatments over right-sided ones, indicating that treatment decisions should be based on individual patient characteristics and molecular profiling.[8,23,24]

MMR/MSI

Immunotherapy with checkpoint inhibitors (such as pembrolizumab, nivolumab, ipilimumab, and dostarlimab-gxly) represents a paradigm shift in the treatment of patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) mCRC, offering durable responses and prolonged survival benefits for a significant subset of patients.[25-28] These therapies are now included in treatment guidelines and are increasingly recognized as standard options for eligible patients in the first-line and subsequent settings. Universal MMR or MSI testing is recommended for all newly diagnosed patients with colon cancer to help inform use of immunotherapy and screen for Lynch syndrome.[8] Testing for MSI may be completed by polymerase chain reaction (PCR) or, preferably NGS panel, as this can also test patients with metastatic disease who require genotyping of RAS and BRAF. Germline mutations in MMR genes, resulting in Lynch syndrome, account for 2% to 4% of CRC cases. Somatic MMR deficiencies are observed in approximately 19% of CRC tumors, while somatic hypermethylation of MLH1 genes may affect up to 15% of colon tumors.[29,30] In the KEYNOTE-177 trial utilizing pembrolizumab monotherapy as first-line treatment for patients with mCRC, the 2- and 5-year PFS rates were 48% and 34%, respectively.[25] The 64-month follow-up from the CheckMate 142 trial, revealed a median PFS that had not been reached with the use of nivolumab alone or with ipilimumab, with 55% of patients progression free and 67%

alive at 5 years.[26] The use of immunotherapy combined with nivolumab and ipilimumab resulted in a significant benefit of mPFS in the initial reported results of the phase 3 CheckMate 8HW study. The 24-month PFS rate was 72% with immunotherapy vs 14% in the chemotherapy arm.[27,28] While generally well tolerated and better than chemotherapy, use of immune checkpoint inhibitors requires close monitoring since their use can lead to immune-related adverse events such as colitis, dermatitis, hepatitis, and endocrine dysfunction.[8] Notably, death from immune-related myocarditis has been observed in several of the immunotherapy studies. While rare, there are no clear risk factors for who may develop this severe toxicity.[28]

Pathologic variants of the polymerase genes, *POLE* and *POLD1*, occur in 2% to 8% of patients.[31,32] Proficient mismatch repair (pMMR) CRC with *POLE/POLD1* pathologic variants has an ultrahypermutated phenotype with a TMB far in excess of what is observed with MSI CRC. Presence of *POLE/POLD1* has shown to predict a favorable response to immunotherapy, with an observed OS of 34 months, more than doubling that of the nonmutated group.[8,33,34]

BRAF V600E Mutations

Approximately 9% of patients with mCRC express a mutation in BRAF V600E.[35,36] In addition to NGS panels, BRAF V600E mutation testing through immunohistochemistry (IHC) is also an option. BRAF mutations are mutually exclusive of RAS mutations. Due to constitutive activation of the mutated BRAF protein product, EGFR inhibition by cetuximab or panitumumab is bypassed. The ineffectiveness and lack of durability of BRAF monotherapy suggest that multi-pathway blockade, rather than reliance on BRAF inhibition alone, is crucial for enhancing response to cetuximab or panitumumab in mutated BRAF tumors, potentially through combination with agents like encorafenib.[37,38] In patients with mCRC in the BEACON CRC trial, use of encorafenib in combination with cetuximab resulted in an improved OS (9.3 months). Most common toxicities associated with encorafenib included fatigue, nausea, diarrhea, and rash.[39]

HER2 Mutations

HER2 is rarely amplified or overexpressed (~3%) in patients with CRC and can be tested using IHC, fluorescence in situ hybridization (FISH) or NGS.[8,40] In patients with mCRC who overexpress HER2 and are RAS/BRAF wild-type, HER2- targeted therapy with trastuzumab, pertuzumab, lapatinib, and/or tucatinib is recommended.[8] CRC with HER2 amplification is more likely to have brain metastasis and tucatinib has activity across the blood-brain barrier. Fam-trastuzumab deruxtecan-nxki is only indicated for patients that express HER2-amplified mCRC tumors (IHC 3+) based on the DESTINY-CRC02 trial, which showed an ORR of 46.9% and duration of response (DOR) of 5.5 months.[41] Notably, this is the only current agent with reported activity after exposure to prior anti-HER2 therapy. Common side effects with anti-HER2 targeted therapy include diarrhea, rash, hepatoxicity, and infrequent—yet severe—cardiotoxicity, interstitial lung disease, and myelosuppression. HER2-targeted therapies are recommended as subsequent therapy options for patients with mCRC after failed chemotherapy or if intensive therapy is not recommended.[8] Ado-trastuzumab emtansine does not currently have a defined role in the treatment of mCRC.

KRAS G12C Mutations

Studies show that about 40% of patients with mCRC have KRAS mutations.[42,43] Patients with a known KRAS-or NRAS-mutant tumor should not be treated with EGFR inhibitors, such as cetuximab or panitumumab. An exception to this is when these agents are given in combination with sotorasib or adagrasib for patients with tumors expressing a KRAS G12C mutation, which are identified in about 3% of all patients with CRC. Toxicities with sotorasib and adagrasib include diarrhea, fatigue, skin reactions, hepatotoxicity, neurological symptoms, and cardiotoxicity.[8,42,43] Other agents targeting specific RAS mutations are in development.

NTRK Mutations

Less than 1% of patients with CRC carry the NTRK gene fusions.[44,45] Typically, these tumors are also KRAS, NRAS, and BRAF wild-type. NTRK inhibitors have been shown to have activity only in patients with NTRK fusions and not point mutations. For patients with an NTRK gene fusion, larotrectinib, entrectinib or repotrectinib are possible options as subsequent therapy. Patients may experience fatigue, nausea, diarrhea, dizziness, cognitive impairment, and hepatoxicity with the use of these agents.[8]

RET Fusions

RET fusions are rarely seen in patients with CRC, estimated to be less than 1%.[46] The presence of activating RET fusions can be identified through a variety of techniques, including IHC, FISH, PCR, and either DNA-or RNA NGS assays.[47,48] Selpercatinib, a kinase inhibitor, may be used for patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on therapy or have no alternative treatment options based on the results of the LIBRETTO-001 trial, which showed an ORR of 43.9%. The most common toxicities included hypertension, fatigue, and diarrhea.[49]

Subsequent Lines of Therapy

There are significant unmet medical needs in patients with mCRC due to limitations in 5-fluorouracil-based chemotherapy, as patients often experience disease progression and significant treatment-related issues. Patients with mCRC who progress on first-line therapy require careful consideration for subsequent treatment options. The approach depends on several factors, including the molecular profile of the tumor, prior treatments received, and individual patient characteristics. The initial priority is determining the MSI status

before proceeding with any further assessments or decisions. For those with wild-type KRAS/NRAS/BRAF tumors who progressed on first-line therapies not including an EGFR inhibitor, options may include cetuximab or panitumumab in combination with chemotherapy (such as FOLFIRI or irinotecan) or as monotherapy.[8]

If patients progress on oxaliplatin-based therapy, irinotecan-based therapy can be considered, and vice versa. For patients with wild-type KRAS/NRAS/BRAF tumors who progress on therapies without an EGFR inhibitor, alternative treatments include cetuximab or panitumumab plus irinotecan, FOLFIRI, or as monotherapy.[8] These therapies are coupled with toxicities such as skin rashes, diarrhea, electrolyte imbalances, and infusion reactions, requiring frequent monitoring and supportive care management.[8,20,22]

After failure of the standard cytotoxic agents, there are multiple approved agents for more refractory disease, including trifluridine/tipiracil, regorafenib or fruquinitinb. Trifluridine/tipiracil, which combines a nucleoside metabolic inhibitor and a thymidine phosphorylase inhibitor, is a therapeutic option for patients with mCRC who have progressed through 2 prior regimens. The RECOURSE phase 3 trial demonstrated that treatment with trifluridine/tipiracil prolonged OS approximately 2 months compared to placebo in patients with mCRC who had previously received standard therapies.[50] Although the improvement in OS was significant, this agent typically is reserved for use in patients who do not have mutations for targeted therapy and have progressed through other chemotherapy agents.[8] Most common side effects with trifluridine/tipiracil include neutropenia, fatigue, nausea, and diarrhea.[50] These agents were initially approved compared to placebo, so the exact preferred sequencing of use is not known. Treatment selection is often based on the side effect profile and residual toxicities. Newer data, including the phase 3 SUNLIGHT trial, suggest the combination of trifluridine/tipiracil with bevacizumab is an option for patients with refractory mCRC, due to the dual-targeted approach aiming to enhance treatment efficacy and potentially overcome resistance mechanisms seen with single-agent therapies.[51,52]

Immunotherapy has emerged as a promising option for first- or subsequent-line treatment in patients with MSI-H/dMMR tumors, with improved survival and quality of life compared to chemotherapy. Patients who express mutations in POLE/POLD1 have shown a favorable response to immunotherapy, resulting in improved OS. Additionally, other targeted therapies provide a less cytotoxic alternative depending on the patient's mutational status, especially if the patient is not a candidate for immunotherapy (MSS/pMMR).

Key concepts

To improve the quality of life and outcomes for patients with mCRC, comprehensive strategies for choosing therapy are essential. These include thorough molecular profiling, employing precision medicine, involving patients through education and shared decision-making, and carefully monitoring and adjusting doses based on tolerability and toxicity. Treatment sequencing should be tailored to each patient, considering their tolerance levels, treatment history, and comorbidities, ensuring a personalized approach to maximize therapeutic benefits while minimizing adverse effects. By integrating these personalized approaches with existing strategies, healthcare providers can enhance the effectiveness and overall outcomes with targeted therapies for patients with mCRC.

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