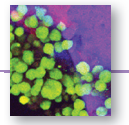

Molecular Profiles Guide Colorectal Cancer Treatment

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An improved understanding of colorectal cancer as a collection of multiple cancer subtypes is paving the way to precision medicine-based treatments.

Colorectal cancer (CRC) is the third leading cause of cancer-related death in veterans, despite significant advances in treatment options.[1,2] Over the past 20 years, the median survival of patients with metastatic CRC (mCRC), has improved with the most recent clinical trials demonstrating a median overall survival (OS) of up to 29 months.[3]

In addition to standard chemotherapeutic regimens using 5-fluorouracil, oxaliplatin, and irinotecan, biologic therapies have resulted in improved OS for patients with mCRC. These therapies include the human vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and the epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab. Additional agents, including aflibercept, ramucirumab, regorafenib, and TAS-102, also have been FDA approved for mCRC, though the OS benefit for these agents as part of the series of standard-of-care treatments is less clear.

Investigators continue to determine subtypes of CRC to further advance treatment options. The histologic classification of colon cancers is actually a collection of multiple cancer subtypes. Each subtype possesses a unique biology largely dependent on the mutations present within the cancer. Recent data, reviewed below, indicate predictive and prognostic benefits to understanding the unique mutational profile of mCRC. Here, the authors present a brief updated summary of these biomarkers and a discussion of treatment strategies.

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RESISTANCE TO ANTI-EGFR THERAPIES

KRAS and *NRAS* are members of the *RAS* family of oncogenes. Activating mutations in these genes results in the propagation of growth factor signals independent of EGFR. The most common *KRAS* mutations are found in exon 2 (codon 12 or 13). Numerous studies over the past 10 years have confirmed that *KRAS* mutations at exon 2 predict resistance to cetuximab and panitumumab.[4-11] Since at least 2009, restricting use of cetuximab and panitumumab has been the standard of care for patients with *KRAS* exon 2 wild-type cancers.[12]

Recent investigations have indicated a predictive role for extended-spectrum *KRAS* and *NRAS* mutations (*KRAS* mutations at exons 2, 3, and 4 and *NRAS* mutations at exons 2, 3, and 4). In the OPUS clinical trial, patients whose cancers possessed extended-spectrum *RAS* mutations received no benefit with the addition of cetuximab to standard chemotherapy in response rate (RR), progression-free survival (PFS), or OS compared with standard chemotherapy alone.[13] Interestingly, median OS was shorter for those treated with cetuximab when a *RAS* mutation was present, though the difference was not statistically significant. Additional studies also have confirmed similar benefits in different settings.[8,14-18]

The CALGB/SWOG 80405 phase 3 clinical trial investigated the first-line use of biologic therapies in combination with standard chemotherapy. The extended-spectrum *RAS* testing from this study now has been

presented.[3,19] In the *RAS* wild-type population, the median OS was 31.2 months in the chemotherapy plus bevacizumab arm and 32.0 months in the chemotherapy plus cetuximab arm (no significant difference). No difference in PFS was observed. A significant improvement in the RR was seen in the cetuximab arm for the *RAS* wild-type population.

Predictive Biomarkers

BRAF is an oncogene in the RAF gene family that encodes a serine-threonine protein kinase found in the Ras-Raf-MAPK cascade. About 10% of CRC harbor a *BRAF* mutation.[20,21] The most significant and prevalent mutation occurs at the kinase domain from the single substitution V600E. Numerous clinical studies have suggested the presence of this mutation as a predictor of resistance to anti-EGFR therapies and a marker of poor prognosis.[6,17,22-25] In a retrospective analysis of *RAS* and *BRAF* mutation status of PRIME study data, patients without *RAS* and *BRAF* mutations showed significantly better OS and PFS when treated with FOLFOX4 (5-fluorouracil, oxaliplatin, and leucovorin) plus panitumumab, compared with FOLFOX4 alone.[8] The presence of *BRAF* mutations in *RAS* wild-type patients resulted in a worse outcome. Treatment with anti-EGFR therapy did not significantly improve median PFS or OS.

***PIK3CA* mutations**. Phosphoinositide 3-kinase (PI3K) is a lipid kinase important for multiple cellular processes including cell growth, proliferation, survival, and apoptosis. *PIK3CA* encodes the catalytic subunit and is mutant in about 20% of mCRC.[26] The PI3K is downstream of EGFR signaling; activation of this pathway in the setting of an oncogenic mutation might lead to resistance to anti-EGFR therapies. Sartore-Bianchi and colleagues examined 110 patients with mCRC treated with either panitumumab or cetuximab.[27] Of these, 15 patient cancers featured *PIK3CA* mutations, and none of these responded to anti-EGFR therapies. In addition, preclinical studies have demonstrated that targeting CRC downstream of PI3K might result in significant treatment benefit.[28,29]

Human epidermal growth factor receptor 2 (HER2) amplification. A subpopulation of CRC with amplification of HER2, a growth factor receptor commonly used in selecting treatment options in breast cancer, has recently been described. The HERACLES phase 2 study evaluated dual HER2 targeting with lapatinib and trastuzumab in therapy-refractory mCRC with HER2 amplification.[30] A RR of 35% was observed in this treatment-refractory population.

***BRAF* mutations**. In addition to predicting a poor prognosis and resistance to EGFR-directed therapies, *BRAF* mutations might be predictive of treatment response using combination regimens containing RAF inhibitors. A recent phase 1B study of a combination therapy using the BRAF inhibitor vemurafenib with irinotecan and cetuximab observed a partial RR of 35%.[31] This is being investigated further in the Southwest Oncology Group 1406 phase 2 trial.

Mismatch repair deficiency. Detection of microsatellite instability or the presence of mismatch repair deficiency has become standard-of-care testing for CRC. This is important for the detection of Lynch syndrome and predicting potential resistance to adjuvant 5-fluorouracil in the adjuvant setting.[32,33] A recent clinical trial has demonstrated benefits for the use of programmed death 1 (PD-1) inhibitors in the setting of mismatch repair deficiency, including a RR of 40% and PFS of 5.4 months.[34]

DISCUSSION

Metastatic CRC is now better understood as a collection of multiple cancer subtypes based on mutational profile. This improved understanding of the biology of CRC is altering treatment strategies to a precision medicine-based approach. It is now the standard of care for all patients with mCRC to have the cancers assayed for mutations in *KRAS* (exons 2, 3, and 4), *NRAS* (exons 2, 3, and 4), and *BRAF*. Anti-EGFR therapies should not be used for patients with *RAS* or *BRAF* mutations outside of a clinical trial because of a demonstrated lack of benefit in all lines of therapy. Currently, there is no evidence that these mutations significantly alter the response to the approved anti-angiogenic agents bevacizumab, aflibercept, ramucirumab, and regorafenib.

The timing of EGFR-directed therapies for patients with wild-type *KRAS*, *NRAS*, and *BRAF* is still being debated. According to the available data, first-line treatment with anti-EGFR agents in combination with FOLFOX or FOLFIRI (5-fluorouracil, irinotecan, and leucovorin) should be considered for all patients with *KRAS*, *NRAS*, and *BRAF* wild-type mCRCs. The toxicities of anti-EGFR therapies also should be considered for this setting, as

some patients find that the acneiform rash, fatigue, nausea, and diarrhea that occur with these agents can have a negative impact on quality of life. As there is no improvement in OS with first-line anti-EGFR therapies for these patients, the increased toxicity from these agents limits their use. In addition, patients with mCRC with known *PIK3CA* mutation should consider use of EGFR-directed therapies only in the later line setting.

Research is focused on how to best use the mutational profile of the tumor to tailor therapies for mCRC. High-quality, large-volume data sets will become more important as molecular subtypes of cancer become more narrowly defined and less common. Further investigations are needed to look for other markers of resistance and to identify biomarkers predictive of treatment sensitivity.

This is an exciting time in the treatment of many cancers, especially mCRC, which significantly impacts the veteran population, because routine DNA sequencing of patient samples has allowed for rapid advances in the realization of precision medicine. This allows for improved patient selection to reduce costs and toxicities while increasing the benefit for veterans. ●

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