ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Factors Guiding Selection of Treatment in Metastatic Colorectal Cancer

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H&O What factors guide selection of treatment in metastatic colorectal cancer?

LS Metastatic colorectal cancer is a very broad area that requires an individualized approach to management. For each case, physicians must consider the disease characteristics, the treatment goals, and how to present the therapeutic options to the patient. A patient who initially presents with synchronous primary and metastatic disease will likely require systemic therapy rather than resection of the primary tumor as a first maneuver, unless the primary tumor is causing significant obstructive symptoms. Patients with a small number of metastases limited to 1 organ (oligometastatic disease) are candidates for curative-intent resection. In general, patients are now characterized into 2 groups: those with disease that is mismatch repair–proficient, or microsatellite stable, and those with disease that is mismatch repair–deficient, or microsatellite instable. The treatment options, approaches, and prognoses are radically different for these groups. Up to 97% of patients with metastatic disease are mismatch repair–proficient (microsatellite stable). These patients do not benefit from currently available immunotherapy approaches. In contrast, current immunotherapies are likely to benefit the small percentage of patients with metastatic colorectal cancer whose disease is mismatch repair–deficient (microsatellite instable). This immunotherapy-eligible group makes up approximately 3% to 4% of patients with metastatic colorectal cancer.

After separating patients into these categories, the next consideration is the extent of their disease. A patient may have widespread metastatic disease or oligometastatic (locoregional) disease. Oligometastatic disease refers to a small amount of tumor in a single organ that is potentially amenable to surgery with curative intent. Widespread disease is treatable, but not realistically curable in the vast majority of cases.

> For patients with mismatch repair–deficient disease, immunotherapy has a relatively high response rate, and the responses are often durable.

H&O What are some of the treatments currently available for metastatic colorectal cancer?

LS Patients with mismatch repair–proficient disease will receive systemic chemotherapy, typically as a first maneuver and possibly in later lines of therapy. The most commonly used regimens are folinic acid (more commonly known as leucovorin), fluorouracil (5-FU), and oxaliplatin (FOLFOX); folinic acid, 5-FU, and irinotecan (FOLFIRI); and capecitabine and oxaliplatin (CAPOX). Treatment with folinic acid, 5-FU, irinotecan, and oxaliplatin

(FOLFIRINOX) is another option for those patients with an Eastern Cooperative Oncology Group performance status of 0. FOLFOX, FOLFIRI, and FOLFIRINOX are administered intravenously, often in an every-other-week schedule and utilizing a 48-hour protracted infusion of 5-FU. In the CAPOX regimen, oxaliplatin is administered at a higher dose once every 3 weeks, so that the aggregate dose of oxaliplatin over a 6-week period is the same in all of these regimens. Capecitabine is administered orally twice a day for 2 weeks on and 1 week off.

For patients with mismatch repair–deficient disease, first-line therapy will often involve the use of a programmed death receptor 1 (PD-1) inhibitor. Pembrolizumab (Keytruda, Merck) is the only PD-1 inhibitor thus far to receive approval from the US Food and Drug Administration (FDA) for the frontline treatment of these patients. Other PD-1 inhibitors are approved for patients with relapsed/refractory metastatic colorectal cancer. It is highly unlikely, however, that the currently available PD-1 inhibitors have any meaningful differences in their activity and toxicity profiles. Therefore, I would expect that any PD-1 inhibitor would be a reasonable choice as first-line therapy for patients with metastatic mismatch repair–deficient colorectal cancer. In the registration study for pembrolizumab in this setting, it was noteworthy that cytotoxic chemotherapy conferred better efficacy in the first 6 months, whereas pembrolizumab led to better outcomes in the long-term. There is therefore room for individualization when selecting treatment for these patients, and some patients are more likely to benefit from cytotoxic chemotherapy up front.

There is also the question of whether a PD-1 inhibitor should be used alone or in combination with another immunotherapy in patients with metastatic, mismatch repair–deficient disease. For example, nivolumab (Opdivo, Bristol Myers Squibb) can be used alone or with ipilimumab (Yervoy, Bristol Myers Squibb), a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor. Ongoing head-to-head clinical trials are comparing single-agent nivolumab vs nivolumab plus ipilimumab. However, since both approaches have already received approval from the FDA, at least in the second-line setting, it has been difficult to accrue patients to clinical trials.

H&O How effective are these treatments?

LS For patients with mismatch repair–deficient disease, immunotherapy has a relatively high response rate, and the responses are often durable. Up to 10% of patients achieve a complete clinical response, which, if durable over time, may realistically be considered a curative result. For patients who have metastatic, unresectable mismatch repair–proficient disease, chemotherapy can extend survival and improve quality of life. However, treatment in such a setting is not realistically curative.

H&O What are the unmet needs in metastatic colorectal cancer?

LS The vast majority of patients with metastatic colorectal cancer will die of the disease. After we have exhausted fluoropyrimidines, oxaliplatin, irinotecan, and—in molecularly selected subsets of patients, epidermal growth factor receptor (EGFR) inhibitors with or without BRAF inhibitors and human epidermal growth factor receptor 2 (HER2)-targeted therapies in those rare patients with tumors that are HER2-amplified and *RAS/BRAF* wild-type—many patients still require another option. Numerous clinical trials are underway to identify better treatment options. Unfortunately, better options are not currently available.

H&O What are the challenges in developing new treatments for metastatic colorectal cancer?

LS A big challenge is that we simply do not have good-enough drugs that show meaningful activity. Another problem seen across the spectrum in oncology is that clinical trials are typically designed for patients in good shape, who have a good performance status, as well as adequate renal, hepatic, and bone marrow function. All too often, patients who have exhausted the standard treatment options no longer meet eligibility for enrollment in clinical trials. Exclusion from enrollment creates frustration and disappointment among patients, who often believe that a clinical trial will provide access to a new treatment with proven efficacy. In reality, of course, clinical trials evaluate the potential efficacy of a new treatment. In our experience, benefit from clinical trials after exhaustion of standard care has been extremely rare in colorectal cancer patients, as described in a 2020 study published in the *Journal of the National Cancer Institute*.

H&O Are there any recent insights into the disease pathology of metastatic colorectal cancer that might help inform the development of new treatments?

LS Researchers have made some modest inroads in identifying some of the molecular subtypes of colorectal cancer that can help guide treatment selection. Up to 8% of colorectal cancer is driven by a mutation in the *BRAF* gene, specifically the *BRAF* V600E mutation. For these patients, there are therapies that can offer benefit, albeit a limited amount. The average improvement in survival compared with the standard of care is just a few months.

The EGFR inhibitors cetuximab (Erbitux, Lilly) and panitumumab (Vectibix, Amgen) are active in left-sided tumors that are wild-type for the *KRAS*, *NRAS*, and *BRAF* mutations and not amplified for HER2. Patients with the HER2 amplification but without mutations in *KRAS*, *NRAS*, or *BRAF* can benefit from dual HER2-targeted therapies (trastuzumab plus pertuzumab [Perjeta, Genentech] or lapatinib) or fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo/AstraZeneca).

The identification of small subsets of patients with a specific vulnerable molecular profile has therefore contributed to treatment advances. However, with the rare exception of the complete responses seen with immunotherapy among patients who are mismatch repair–deficient, these advances offer only modest improvement, with perhaps a few extra months of disease control. These regimens are not improving the cure rate, which is of course what patients are looking for.

H&O Where should future research focus?

LS Tremendous advances in immuno-oncology have helped patients with colorectal cancer who are mismatch repair–deficient, as well as patients with melanoma, kidney cancer, lung cancer, and other malignancies. A great frustration in colorectal cancer is that the overwhelming majority of patients are unable to benefit from immunotherapy. More work must be done to learn how to make colorectal cancers vulnerable to immunotherapeutic approaches. So far, this goal has been difficult to achieve.

Disclosure

Dr Saltz is a paid consultant for Genor Biopharma Ltd.

Suggested Readings

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