CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Immunotherapy in Colorectal Cancer

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H&O Is colorectal cancer (CRC) a good target for immunotherapy?

DL A subset of patients with CRC have tumors that are found to be deficient in DNA repair proteins, a condition referred to as mismatch repair deficiency or microsatellite instability (MSI). Such tumors respond to immunotherapy. MSI is present in 15% to 20% of all CRCs and in 4% to 6% of metastatic CRCs (Figure). Although MSI is often found in patients with hereditary nonpolyposis CRC, or Lynch syndrome, it is most often caused by somatic alterations in a tumor.

Most patients with CRC have tumors that are mismatch repair proficient or microsatellite stable, however. No approved agent or combination of immunotherapy agents is available to treat these tumors, although many studies are under way. Within the larger population of patients who have microsatellite-stable tumors, the pattern of immune cells or inflammatory infiltrates is heterogeneous. Therefore, the underlying immunologic milieu in different subtypes of microsatellite-stable tumors will likely require different targeting methods.

The levels of baseline T-cell infiltrates in tumors with a high degree of microsatellite instability (MSI-H tumors) and in tumors that are microsatellite stable have prognostic implications, suggesting that the immune system likely plays a role in a subset of tumors that are microsatellite stable.

H&O Why are tumors with MSI more likely to respond to immunotherapy?

DL Tumors that are deficient in mismatch repair proteins are unable to repair mismatches that occur during DNA repair. Because of this deficiency, mutations accumulate. The more mutations that occur, the higher the probability that a tumor will create neoantigens that the immune system can be recognize.

H&O How can oncologists identify which tumors are more likely to respond to immunotherapy?

DL Mismatch repair–deficient tumors can be identified by immunohistochemical stains showing deficient or missing mismatch repair proteins (MLH1, MSH2, MSH6, or PMS2), or by a polymerase chain reaction–based test. MSI-H status is caused by shifts resulting from the accumulation of errors in repetitive DNA sequences. MSI status is also reported on next-generation sequencing panels. A sequencing report with an increased number of reported mutations is another clue that a tumor is hypermutated and is an MSI-H cancer.

H&O What types of immunotherapy have been investigated for use in CRC?

DL The programmed death 1 (PD-1) inhibitors are one major class of agents that have been investigated in CRC. Pembrolizumab (Keytruda, Merck) has been approved for any mismatch repair–deficient or MSI-H solid tumor, and nivolumab (Opdivo, Bristol-Myers Squibb) has been approved for MSI-H CRC.

For MSI-H CRCs, single-agent PD-1 inhibitors are effective. Durable responses, some now lasting over 3 years, have been seen in patients with advanced treatment-refractory cancers.

For microsatellite-stable tumors, PD-1 inhibitors have not been active as single agents. Even in KEYNOTE-028 (Study of Pembrolizumab in Participants With Advanced Solid Tumors), in which the patients with CRCs selected

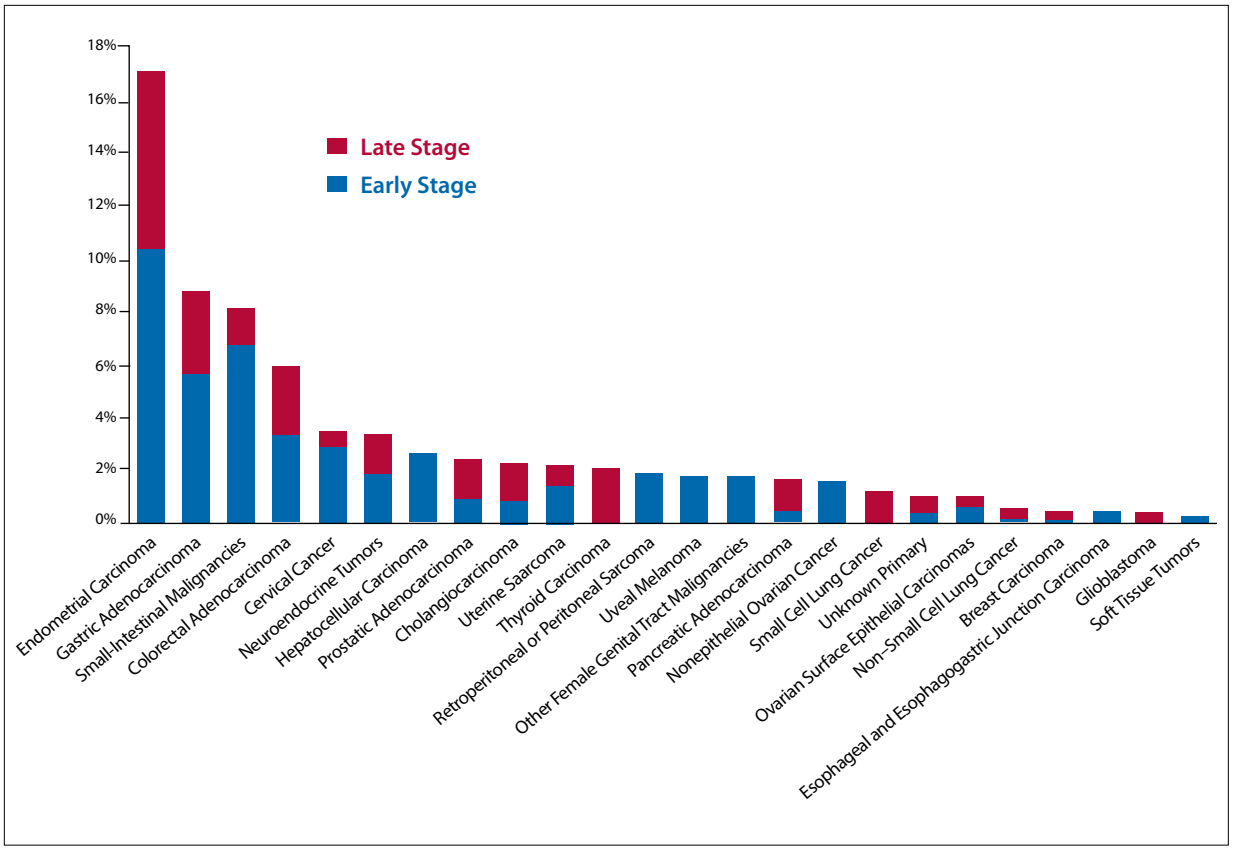

Figure. Mismatch repair deficiency across 12,019 tumors. The proportion of mismatch repair–deficient tumors in each cancer subtype is expressed as a percentage. Mismatch repair–deficient tumors were identified in 24 of 32 tumor subtypes tested, more often in early-stage disease (defined as a stage earlier than stage IV).

Source: Le DT et al. *Science*. 2017;357(6349):409-413. Republished with permission.

for programmed death ligand 1 (PD-L1) positivity, there was little activity in those treated with pembrolizumab. The single response was in a patients with an MSI-H CRC. This finding supports the hypothesis that PD-L1 is not a good selection marker for CRC.

H&O What are the most important studies that have looked at immunotherapy in patients with CRC?

DL The 2 most important studies are KEYNOTE-016 (Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable Tumors) and CheckMate 142 (An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread).

KEYNOTE-016, a study led by Johns Hopkins that was published in the *New England Journal of Medicine* in 2015, was the first study to report the activity of PD-1 inhibition in MSI-H cancers. In this phase 2 study, which included 28 patients with progressive metastatic CRC, the patients received intravenous pembrolizumab at a dosage of 10 mg/kg every 14 days. After a median follow-up of 20 to 36 weeks, the objective response rate was 40% in patients with mismatch repair deficiency vs 0% in those without mismatch repair deficiency. The disease control rates were 90% vs 11%, respectively. Updated data were presented in *Science* in 2017 that confirmed durable responses across multiple tumor types.

Global studies are ongoing as well. In CheckMate 142, a phase 2 study, nivolumab was given to 74 patients in 8 countries who had recurrent or metastatic CRC that was MSI-H. All patients had received at least one previous line of treatment and were given nivolumab at a dosage of 3 mg/kg every 2 weeks until disease progression, death, unacceptable toxic effects, or withdrawal from the study. At a median follow-up of 12.0 months, the objective response rate was 31.1%, and the disease control rate was 69%.

H&O What are the side effects and limitations of immunotherapy?

DL Immunotherapy can cause immune-related adverse events, which present as autoimmune-like toxicities. The most common immune-related events are rashes and pruritus. Patients can also experience endocrine effects and require thyroid hormone replacement. Less common side effects include pneumonitis, hepatitis, and nephritis. Side effects can be managed by pausing treatment or by instituting the use of immunosuppressant agents, such as corticosteroids. Patients with severe side effects probably should not be rechallenged.

H&O How can we make immunotherapy work for a larger percentage of patients with CRC?

DL We have interesting combination studies under way for patients with CRC that is microsatellite stable. These studies are evaluating PD-1 inhibition in combination with chemotherapy, radiation, targeted agents, and bispecific antibodies.

One of the combinations that has received the most attention is MEK inhibition plus PD-L1 inhibition. At the 2016 annual meeting of the American Society of Clinical Oncology, Dr Johanna Bendell presented data on the combination of cobimetinib (Cotellic, Genentech) and atezolizumab (Tecentriq, Genentech). There were 4 partial responses. The tumors of 3 responders were mismatch repair proficient, and the mismatch repair status of 1 patient was unknown. PD-L1 upregulation, CD8 T-cell infiltration, and expression of major histocompatibility complex I were demonstrated by treatment biopsies. The results of this study led to a phase 3 study comparing cobimetinib plus atezolizumab and atezolizumab alone vs regorafenib (Stivarga, Bayer) in patients with previously treated colon cancer (NCT02788279). Although this study has completed enrollment, results are not yet available.

A more recent data set that has received attention involves the use of carcinoembryonic antigen T-cell bispecific antibody (CEA-TCB) in combination with atezolizumab. CEA-TCB binds T cells and tumor cells simultaneously. Preliminary data on the use of CEA-TCB and atezolizumab showed a response in 2 of 11 patients (18%) treated with 80 or 160 mg of atezolizumab (NCT02650713).

H&O Is there a rationale for using immunotherapy in the adjuvant setting?

DL PD-1 and PD-L1 inhibitors may work in patients who have earlier-stage disease with a smaller disease burden and fewer prior treatments. The frequency of MSI is higher in early-stage disease than in later-stage disease, suggesting that the immune system is playing a role in containing this disease. Adjuvant studies in stage II MSI-H disease would likely be difficult to perform given that the prognosis for these patients is quite good even without any additional therapy. However, in stage III disease, the current standard of care is chemotherapy with a 5-fluorouracil/oxaliplatin–based regimen. Therefore, studies in MSI-H stage III disease are warranted and under way. One current study is testing chemotherapy with and without atezolizumab (NCT02912559).

H&O What questions should future research attempt to answer?

DL Many studies of combination therapy in patients with CRC are ongoing or being planned, and we are starting to see low-level but real responses across these studies. Understanding why certain patients respond will help guide the development of new treatment approaches. Comparing the attributes of responding and nonresponding patients is important because CRC is not just one disease, and the different subsets may respond differently to various combinations.

Disclosure

Dr Le has served on the advisory board of and received research funding from Merck and Bristol-Myers Squibb.

Suggested Readings

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