CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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Circulating Tumor DNA as a Marker of Minimal Residual Disease in Colorectal Cancer

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H&O How common is recurrence after surgery for nonmetastatic colon cancer?

SK Most patients with stage II or III colon cancer have a risk for recurrence in the 20% to 30% range, although the risk can be as low as 10% or as high as 50%, depending on the characteristics of the tumor. The recurrence rate is less than 10% for patients with stage I colon cancer.

H&O How effective is adjuvant therapy after surgery for nonmetastatic colon cancer?

SK The use of regimens based on 5-fluorouracil and oxaliplatin can reduce the relative risk for recurrence by as much as half.

H&O Which patients are most likely to benefit?

SK We usually recommend adjuvant therapy for patients with stage III colon cancer and do not use it in patients with stage I colon cancer. Stage II is more complicated because we do not know who is most likely to benefit from adjuvant therapy. We can look at clinical characteristics, such as poorly differentiated histology, the presence of T4 lesions, and lymph node involvement, but these are fairly modest predictors of recurrence.

H&O What is the efficacy rate of adjuvant therapy in patients who have measurable residual disease?

SK Although the rate of benefit is still being determined in larger series, the data we have so far suggest that adjuvant therapy can clear minimal residual disease (MRD) in approximately one-third of cases, which reflects the range of survival benefit we see with long-term follow up after adjuvant therapy.

> Circulating tumor DNA tests are very sensitive, with the ability to detect mutations that appear in just 1 of 100,000 DNA fragments.

H&O What is the best way to detect MRD in these patients?

SK The best technique right now is measurement of circulating tumor DNA (ctDNA), which is more sensitive than imaging tests. ctDNA tests look for mutations in the plasma from a peripheral blood draw. They are very sensitive, with the ability to detect mutations that appear in just 1 of 100,000 DNA fragments. Other tests in development also include tumor epigenetic features.

H&O Can you explain the difference between tumor-informed and tumor-agnostic MRD tests?

SK We have 2 possible approaches to determining whether a patient's cancer is still present in the body. In the tumor-informed approach, we sequence the DNA of a resected tumor and then look for specific mutations that match the tumor profile. In the tumor-agnostic approach, we sequence genes that are commonly mutated in colorectal cancer, but the assay does not incorporate the individual patient's tumor information. The advantage of the tumor-agnostic approach is that testing is less complex and can be done more rapidly. The disadvantage of the tumor-agnostic approach is that we sometimes find alterations that are not coming from the residual disease, so we get a false-positive result.

H&O When should blood samples be taken to detect MRD after surgery?

SK We typically recommend taking blood samples at least 2 to 3 weeks after surgery to allow time for healing after surgery. Owing to the inflammation and tissue healing that occur after surgery, a large amount of normal DNA is released into the circulation, which makes the detection of abnormal DNA immediately after surgery more difficult. We take blood samples again after adjuvant therapy, and then again during surveillance.

H&O If a patient has a negative MRD test result and no adjuvant treatment is given, should adjuvant treatment be initiated if the MRD test result is positive on sequential testing?

SK We do not know the answer to that question at the moment, but we are designing studies to try to find out. The hope is that we may be able to use adjuvant therapy to cure the disease at a later point even if we withhold adjuvant therapy initially.

H&O Could the conversion rate of ctDNA from positive to negative someday be used as an endpoint in trials of adjuvant therapy?

SK We hope that this may be the case someday. The current understanding is that ctDNA clearance must occur for cure to take place, but clearance alone does not guarantee that the disease will not recur. Clearance of ctDNA is a good endpoint for looking at the activity of a therapy, but much more research will be required to validate it as a formal surrogate endpoint. We do not yet know how well ctDNA clearance translates into improvements in disease-free survival and overall survival. Right now, ctDNA clearance is being used in small proof-of-principle studies to see if it produces signals of activity for novel therapies.

H&O What are some of the notable trials that are using clearance of ctDNA as a potential endpoint?

SK My group is conducting a single-arm, phase 1b/2 study of 15 patients with colorectal cancer who have detectable ctDNA and no evidence of radiographic disease (NCT03436563). All patients are receiving an inhibitor of transforming growth factor beta and programmed death ligand 1, and we are looking at the objective response rate along with clearance of ctDNA. Another phase 2 study of interest will be looking at a messenger RNA–based vaccine called RO7198457 in patients with ctDNA-positive stage II or III colorectal cancer (NCT04486378). Finally, the phase 2/3 COBRA study from NRG Oncology is looking at how well ctDNA can predict which patients with stage IIA colon cancer will benefit from treatment (NCT04068103).

Clearance of ctDNA is a good endpoint for looking at the activity of a therapy, but much more research will be required to validate it as a formal surrogate endpoint.

H&O What other biomarkers have the potential to aid in detecting MRD?

SK As previously mentioned, a lot of the ctDNA research is focused on tumor mutations, but researchers are also interested in looking at tumor methylation because methylation can be specific to cancer and improve testing sensitivity. Another approach is looking at DNA fragment sizes. Regardless of the DNA content, the size of the DNA fragments from cancer cells may be different from the size of fragments from normal, healthy cells.

H&O What questions remain to be answered when it comes to ctDNA?

SK We still need to know what the best assay is for

testing, and how often we should be testing. Even more importantly, what do we do for patients who have received all their adjuvant therapy but are now ctDNA-positive? What novel therapies can we deploy in that space to potentially cure them?

H&O What approach do you use personally in terms of which assay to use and how often to test?

SK Until recently, we were using our own in-house ctDNA assay. Now we are using a tumor-informed assay called Signatera, made by Natera, to test our patients every 3 months. Although Signatera is the only commercially available assay at the moment, we know that more are coming because a number of additional assays are in development. Many institutions have developed or are developing their own in-house assays as well.

H&O What other advice do you have regarding the use of ctDNA assays?

SK The multidisciplinary Colon and Rectal-Anal Task Forces of the United States National Cancer Institute published a consensus statement on ctDNA testing in colorectal cancer in *Nature Reviews Clinical Oncology* in July of this year. Our task was to summarize current data on the utility of ctDNA testing in the management of colorectal cancer and to provide guidance in promoting the efficient development and integration of this technology into clinical care. One of the points we emphasized is that the selected assay must be appropriate for the application—that is, you need to choose a different assay depending on whether the result might cause you to withhold therapy or to escalate treatment.

H&O What other benefits do you expect to see from ctDNA assays?

SK These assays have tremendous potential for use in novel drug development. Previously, we have not been able to move many novel therapies into the adjuvant setting because treatment is so complex and the studies need to be so large. I expect ctDNA testing to be a game changer because it will allow us to determine whether a particular agent is worth pursuing on the basis of a 20-patient study rather than a 1000-patient study.

Disclosure

Dr Kopetz holds stock or other ownership interests in MolecularMatch, Navire, and Lutris; has served in a consulting or advisory role to Roche, Genentech, EMD Serono, Merck, Karyopharm Therapeutics, Amal Therapeutics, Navire Pharma, Symphogen, Holy Stone, Biocartis, Amgen, Novartis, Lilly, Boehringer Ingelheim, Boston Biomedical, AstraZeneca/MedImmune, Bayer Health, Pierre Fabre, EMD Serono, Redx Pharma, Ipsen, Daiichi Sankyo, Natera, HalioDx, Lutris, Jacobio, Pfizer, Repare Therapeutics, Inivata, and Inivata; and has received institutional research funding from Sanofi, Biocartis, Guardant Health, Array BioPharma, Genentech/Roche, EMD Serono, MedImmune, Novartis, Amgen, Lilly, and Daiichi Sankyo.

Suggested Readings

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