ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Microsatellite Instability in Colorectal Cancer

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H&O What is DNA mismatch repair, and how does it relate to microsatellite instability (MSI)?

BGS DNA mismatch repair is the process by which proteins are able to recognize and correct errors that occur naturally in DNA during the process of its own replication. Mismatch repair is impaired if these repair proteins are mutated in a way that makes them nonfunctional, which leads to the accumulation of DNA errors. If one of these unrepaired mutations occurs in, say, the promoter region of a growth regulatory gene, cellular growth is going to proceed unregulated.

Microsatellites are long repeats of short sequences of nucleotide bases. The occurrence of numerous mismatches in these microsatellites can be a sign of impaired DNA mismatch repair; it suggests that something more insidious is going on with some of the other genes.

H&O How common is MSI?

JM MSI refers to a subset of cancers in approximately 10% to 20% of patients with colorectal cancers that arise not through the traditional polyp mechanism, but through this pathway of MSI that Dr Smaglo described above. Some patients have Lynch syndrome, in which they have an inherited predisposition to cancer and may go on to develop hereditary nonpolyposis colorectal cancer (HNPCC). This accounts for about 4% to 6% of colorectal cancers. Other patients—approximately 6% to 14%—do not inherit MSI, but acquire it over time. Recognizing this alternative pathway is important because most of our strategies for reducing colon cancer—such as screening—have been focused on the 80% to 90% of patients who have the traditional polyp mechanism of developing colon cancer.

H&O Do colorectal tumors with MSI have any distinctive characteristics?

BGS Yes. Colorectal tumors with MSI are more likely to occur in the proximal colon, and they tend to have a greater mucinous component. They are often poorly differentiated, which is interesting because poorly differentiated tumors usually have a worse prognosis, but these tumors tend to behave better than one would expect for a poorly differentiated tumor. In addition, these tumors tend to have a lymphocytic infiltrate that is T-cell directed against the specific tumor frameshift peptides that are associated with the MSI.

JM Tumors with MSI have a better prognosis than those that are microsatellite-stable; stage for stage patients appear to do better. Although most of the research has focused on the inherited syndromes, this probably is true for the acquired cases as well. The tumors usually are poorly differentiated; they look aggressive under the microscope and

so the temptation is to think they have a worse prognosis. After molecular profiling is performed and it becomes clear that the tumor has MSI, however, the prognosis is better than you had originally thought.

Another difference is that these tumors typically do not start with a precursor polyp, so there is not that traditional lag time between precancerous changes and cancer. Our standard screening techniques, such as a colonoscopy every 10 years, will not work for these kinds of tumors.

H&O In what ways does MSI testing affect treatment?

BGS MSI is important in the management of stage II colorectal cancer. Patients whose tumors fall into this stage typically are not treated with adjuvant chemotherapy after curative surgery because the additional benefit is small, and is outweighed by the risk of side effects.

With that being said, in the modern era we no longer think that all stage II colorectal cancers are the same; we need to start understanding how these tumors might be different. This is one of the ways in which we can start to personalize our treatment strategy. Despite having a poorer prognosis, tumors that are found to be microsatellite-stable, even in stage II colorectal cancer, respond better to therapy than those that demonstrate MSI.

That knowledge might help us decide which of these stage II patients, who typically do not receive adjuvant chemotherapy, may be high-risk and may benefit from chemotherapy. The final decision will, of course, require a discussion with the patient, but the decision will be based on a bit more information than if you took the same approach to all the tumors based on whether the cancer had spread.

JM The study by Allegra and colleagues that was published in the *New England Journal of Medicine* in 2003 actually suggested that giving adjuvant chemotherapy with fluorouracil to patients with stage II colon cancer whose tumors had MSI was harmful. There are no data to suggest that this approach improves outcome. At our institution, we recommend that no decision be made until we know the patient's microsatellite status. We do not start chemotherapy and wait on the gene test; in stage II colorectal cancer, we do the gene test before we start the chemotherapy.

In stage III colorectal cancer, the choice of treatment is more controversial. The data do not show any benefit of chemotherapy in stage III tumors with MSI, but on the other hand, they do not show harm. There is also a school of thought that we should in fact be giving stage III colorectal cancer patients adjuvant leucovorin, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy regardless of microsatellite status. The idea is that the oxaliplatin helps overcome this issue, and may in fact take advantage of the MSI genetics that Dr Smaglo already described.

The current standard of treatment is not to treat stage II colorectal cancer with adjuvant fluorouracil. I recommend that oncologists consider treating stage III tumors with MSI with oxaliplatin plus a fluoropyrimidine-based therapy.

H&O How long has MSI testing been available?

JM We have been able to measure MSI for a long time, and it has become available to standard clinical practitioners over the last 2 to 5 years. Awareness about it is not great, however, and it is not being done routinely in a lot of practices where we think it needs to be. There is an unmet need on the education side. The test is actually quite difficult and controversial.

H&O Is MSI testing increasing in importance?

BGS Absolutely. As we have discussed, we are starting to understand how to apply the results in a very real way—we are having discussions with our patients about whether or not they would be appropriate for a different treatment.

JM I have a lot of patients who see me for follow-up care approximately 5 years after their diagnosis. I recommend that we go back and test for MSI even in that population, because this has the potential to detect inherited syndromes.

H&O Should all patients' tumors be tested for MSI?

BGS I think it should be tested in all patients, although with a caveat that its direct clinical applicability today is going to be limited to a certain subset of the population. Right now, the ability to make that information clinically applicable depends on that individual patient's cancer stage. MSI testing is more likely to inform our discussion about treatment for patients whose tumors are stage II or III than for those whose tumors are stage I or IV.

MSI testing is evolving, however, and what we know today might be different compared with what we know 1 year from now or 5 years from now. We may be able to use the information to help these patients at that time.

JM Right now, we test all patients with a strong family history of colorectal cancer, and I think we are moving toward having all patients tested. The test can be helpful in defining whether or not they have an inherited cancer syndrome. Dr Smaglo pointed out that we make treatment decisions using the test in the stage II and III colorectal tumors, but in all stages we want to make sure we are not missing what is a relatively common inherited syndrome.

H&O Is your approach to MSI testing different from what community-based oncologists are doing right now?

JM I would say that oncologists at major cancer centers are doing MSI testing routinely, whereas most community-based oncologists are not. But if I were making policy and saying what should be covered by all insurance companies, I would recommend that we be more selective and focus on patients who are young or who have a strong family history.

H&O How is MSI testing conducted?

BGS There are 2 different approaches. Polymerase chain reaction (PCR)-based assays detect novel DNA instability in the microsatellites. The other approach is immunohistochemistry, which involves looking for the most commonly lost mismatch repair proteins. Immunohistochemistry tends to be faster and more straightforward than the PCR-based assay. As with any test, however, it only works if we know what we are looking for; we might be missing other proteins that are mutated that we do not know to look for at the present time.

JM The problem is, MSI testing is not black and white. For example, with a given patient we may begin with immunohistochemistry. With this technique, we look for 4 proteins that are responsible for maintaining the microsatellite via DNA repair. What we often get back is a multipage report showing that these proteins are present. Practitioners who do not know what they are doing might think that means that the patient has the mutation. In fact, it means that MSI is not present.

Most institutions start with immunohistochemistry, and if all 4 proteins are present, no more testing is conducted. If it is suspected that a particular patient's tumor might still have MSI, however, or if 1 or 2 of the proteins are missing, the PCR-based technique can be performed. Implementing the immunohistochemistry first is helpful because it lets you know where to focus your PCR testing. Instead of doing the sequencing on everything, you drill down into the genes that code for the missing proteins.

Sometimes we find mutations that we recognize as being responsible for tumors, but other times we find mutations that have not been described before, or whose clinical significance is not understood. We may not know whether a given mutation is causing the tumor or is just a bystander.

This is where testing becomes confusing, even to those of us who have access to genetic counselors. We have to ask ourselves, is the mutation in a particular patient meaningful or not? Sometimes we simply have to decide yes it is or no it is not, which is also the case for mutations like BRCA1. Such uncertainty is not unique to MSI, and it is something we need to be aware of.

H&O How accurate is MSI testing?

JM If you go through the entire process of immunohistochemistry plus PCR testing, we can be certain of our answers in about 90% to 95% of patients.

H&O Is there anything else that you would like to add about MSI testing?

BGS MSI status is just one more piece of information that needs to be applied in the context of the entire patient who is before us. You cannot use MSI testing to be told precisely what to do; the decision needs to address what is appropriate for a particular patient, based on factors like cancer stage and willingness to consider chemotherapy.

As we begin to better understand MSI and are able to narrow down the implications of these different genes, the advice will become more concrete. Right now, it has a very focused utility in our clinical practice, and we always remain aware of how the results fit into the grander scheme of our patient's profile.

Suggested Readings

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