ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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IN FOCUS: Colorectal Cancer

Advances in Defective Mismatch Repair Colon Cancer

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H&O What is microsatellite instability?

DS Microsatellite instability is a term used to describe the presence of mutations in a class of repetitive DNA, called microsatellites. This DNA damage, found in tumor tissue, occurs because of a primary defect in DNA mismatch repair. Mutations are common in DNA. However, a normal cell has a variety of proofreading systems to identify mistakes and correct them before permanent damage can occur. One of these proofreading systems is DNA mismatch repair. In the absence of this proofreading system, DNA damage accumulates; an example is instability at microsatellites. The accumulation of too much DNA damage can result in that cell becoming a cancer cell. For colon cancer, at least 2 different major pathways have now been identified—1 of which is due to the presence of defective mismatch repair. In this discussion, I am focusing on this pathway. Defective mismatch repair tumors are characterized by the presence of accumulated DNA damage, as seen by microsatellite instability. These tumors also demonstrate loss of protein expression for any one of several genes involved in DNA mismatch repair: *MLH1*, *MSH2, MSH6,* and *PMS2.*

H&O What is high-phenotype microsatellite instability?

DS In order to identify colon cancers that have defective DNA mismatch repair, tumor DNA is tested for the presence of microsatellite instability. Most colon cancers (~85%) do not have mutations at any microsatellites tested (called microsatellite stable [MSS]) or instability at just a few (low-frequency microsatellite instability [MSI-L]). However, tumors that have defective mismatch repair—approximately 15% of all colon cancers—have mutations in many or most microsatellites tested. As a result, these tumors are said to have high-frequency microsatellite instability (MSI-H). Only patients who are MSI-H are considered to have defective mismatch repair colon cancer.

H&O What is the difference between defective mismatch repair colon cancer and Lynch syndrome?

DS Lynch syndrome is a genetic predisposition to colon cancer that affects a small percentage of patients with colon cancer (1%-5%); the cancers that arise in these patients are due to defective DNA mismatch repair. However, in these cases, a mutation in any one of several genes involved in DNA mismatch repair (*MLH1, MSH2, MSH6,* and *PMS2*) has been inherited. An existing mutation in one of these genes, which is present in all cells, sets the stage for a more rapid accumulation of DNA damage and a very high likelihood of forming cancer very early in life. However, the majority (>90%) of patients with defective mismatch repair pathway–generated tumors do not have Lynch syndrome. Rather, the majority of patients' defective mismatch repair tumors are sporadic events. That is, the same genes are mutated but this occurred by chance at some point in an individual's life, and the mutations were not inherited. As a result, these individuals tend to have

their tumors later in life, as it has taken much longer to acquire the necessary genetic damage.

H&O Why would a patient be screened for MSI-H?

DS Until my colleagues and I presented our data at the 2008 annual meeting of the American Society of Clinical Oncology, screening for microsatellite instability was usually done to identify patients most likely to have Lynch Syndrome, a hereditary form of colon cancer. If a patient with colon cancer were young or had known relatives with the disease, the physician might have ordered a test for microsatellite instability in order to help make a diagnosis of Lynch Syndrome for that patient. If the test results were negative, the patient would be considered not likely to have Lynch Syndrome, but he or she could still have another hereditary form of colon cancer. If a patient demonstrated microsatellite instability, then the patient's risk for having Lynch Syndrome is increased. However, as many of the patients with MSI-H have sporadic colon cancer and not the hereditary form, further tumor and genetic testing is necessary to distinguish between the 2 possibilities. The relatively simple test for MSI-H was thus used as a screening test to rule out further genetic testing.

H&O What is the next step if a patient's tumor is found to have MSI-H?

DS If a patient is suspected of having a possible hereditary form of colon cancer, MSI-H testing is warranted to gain information as to whether further genetic testing is needed. Until recently, there was no other standard reason to test for microsatellite instability. In our view, the data we presented earlier this year substantially increase the clinical relevance of testing for microsatellite instability. First, we have validated the postulation that patients with MSI-H tumors, or tumors arising from the defective mismatch repair pathway, have better prognosis than patients who do not. Additionally, earlier data, generated in 2003, led to the hypothesis that in patients who have MSI-H colon cancer, the standard treatment of 5-fluorouracil (5-FU) and leucovorin that would be considered for stage II patients may not be effective. Our study confirmed these earlier findings: patients with defective mismatch repair tumors do not benefit from 5-FU–based chemotherapy. In fact, there is a trend toward a poorer outcome when treated. Based on these data, we feel that there is considerable new clinical utility to testing for defective mismatch repair in the group of patients that would typically be considered for treatment with 5-FU and leucovorin (ie, stage II patients). Of stage II patients, approximately 33–40% do receive 5-FU–based chemotherapy. In such patients under consideration for this treatment, defective mismatch repair testing is warranted because if a patient is found to have defective mismatch repair, his or her prognosis is better, and the data strongly indicate that this treatment will not confer benefit.

H&O What explanations for this lack of response to 5-FU–based chemotherapy have been postulated?

DS Overall, it is unknown why these patients do not respond well to 5-FU–based chemotherapy. However, there are 2 hypotheses to explain defective mismatch repair tumors' lack of response to 5-FU–based chemotherapy. First, because MSI-H tumors have problems with DNA repair, the tumors cannot repair mutations induced by chemotherapy, which could potentially cause the cancer to become even more aggressive. Second, MSI-H tumors, in the absence of chemotherapy, produce a strong innate immune response, and it has been thought that this immune response makes these tumors less aggressive in the absence of chemotherapy. When chemotherapy is given, it may interfere with the natural immune response that is holding the tumor in check, allowing the cancer to grow more aggressively. These hypotheses have been generated based on cell lines and laboratory experiments in mice, but there is no proof in humans that these hypotheses are true. There may be other undiscovered explanations as well.

H&O What is the recommended treatment method for a patient with MSI-H colon cancer?

DS Stage II patients, for whom the most data are available, represent the primary setting in which an alternative treatment is needed. Stage I patients have such excellent prognosis regardless of mismatch repair status that adjuvant chemotherapy is not appropriate for them. Stage III patients receive FOLFOX (5-FU, leucovorin, and oxaliplatin [Eloxatin, Sanofi-Aventis]) as standard therapy, and there are insufficient data on response to FOLFOX in patients with MSI-H tumors. There are preliminary data that FOLFOX may overcome the resistance to 5-FU that is associated with MSI-H status, but these data are not well-established and FOLFOX remains standard of care in stage III patients. MSI-H is very rare in stage IV patients (3%). In standard stage II patients, FOLFOX has been shown not to confer benefit. However, as published in *Lancet* in 2007, the combination of 5-FU and leucovorin was shown to have some modest benefit versus control in stage II patients in the QUASAR trial. Therefore, the therapy that would

be considered standard of care in stage II patients, if they are to be treated, would be 5-FU and leucovorin. Our study has shown that patients with stage II disease who have defective mismatch repair tumors will not benefit from this combination. Therefore, we recommended that a physician planning to treat a stage II patient with this combination test the patient for defective mismatch repair. If the patient is found to have a defective mismatch repair tumor by testing for microsatellite instability or by immunohistochemistry for *MLH1* or *MSH2,* after surgery, no further adjuvant therapy, with observation for possible recurrence, is recommended. There are no data to suggest that chemosensitivity after recurrence is affected by mismatch repair status. Thus, MSI-H patients who experience recurrence should be treated as MSS patients.

H&O What aspects of microsatellite instability remain to be further investigated?

DS There are several questions regarding microsatellite instability for future research. First, in stage III patients, does microsatellite instability predict response to FOLFOX? Should stage III patients therefore be subject to testing for microsatellite instability to determine if they are candidates for therapy with oxaliplatin? What is the recommendation regarding the use of other agents in MSI-H patients? For example, data presented in abstract form in 2006 by Bertagnolli and colleagues suggest that adjuvant irinotecan may be active in patients with MSI-H stage III tumors. This large, randomized phase III trial showed a trend toward a benefit from adding irinotecan to 5-FU and leucovorin in these patients. Therefore, whether microsatellite instability plays a role in stage III patients' response to treatment remains to be elucidated. In addition, in the treatment of patients with stage II MSI-H disease, are there therapies other than 5-FU and leucovorin that would provide benefit? If oxaliplatin or irinotecan are effective in patients with MSI-H stage III disease, would these agents be effective in patients with MSI-H stage II disease? Further study is needed in this regard.

H&O Could you discuss contradictory findings regarding the efficacy of 5-FU–based chemotherapy in patients with MSI-H stage II disease?

DS Other studies have come to different conclusions from ours. My colleagues and I set out to confirm our initial findings because they were considered controversial. We feel that our confirmatory data are the most robust data available because we included patients only from randomized clinical trials of 5-FU–based treatment versus surgery alone. Other reports have included groups of patients who were treated and another group of patients who were untreated, and compared outcomes according to microsatellite instability status, but the patients had not been randomized between treatment and no treatment, which allows for substantial selection bias. The treated patients have tended to be younger, more fit, and treated at institutions that offer more aggressive therapy. In the absence of randomization between treatment and control, the ability to draw meaningful conclusions regarding whether a marker predicts treatment efficacy is severely limited. As a result, in our research, we specifically gathered data only from randomized trials conducted around the world. Moreover, these data are very mature. In approximately 1990, it was demonstrated that 5-FU and leucovorin was an effective adjuvant therapy. Therefore, to find patients who were randomized to 5-FU based-treatment versus control, it was necessary to gather data from trials conducted in the 1980s.

Suggested Readings

Bertagnolli MM, Compton CC, Niedzwiecki D, et al. Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, 5-fluorouracil and leucovorin in stage III colon cancer. *J Clin Oncol.* 2006;24(18S pt 1): Abstract 10003.

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Sargent DJ, Marsoni S, Thibodeau SN, et al. Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon cancer (CC): A pooled molecular reanalysis of randomized chemotherapy trials. *J Clin Oncol.* 2008;26:(20S pt 1): Abstract 4008.