Genotypes Guide Treatment for Rectal Carcinoma

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SAN FRANCISCO — Physicians are using patients' genotypes to determine the type of treatment they receive for rectal carcinoma in a Washington University study, with a more aggressive regimen reserved for patients with "bad-risk" genetic profiles.

The strategy appears to have paid off so far, with significantly improved outcomes for a subgroup of patients predicted to do poorly on the basis of polymorphisms of a pivotal gene, reported Dr. Benjamin R. Tan, a medical oncologist at Washington University in St. Louis.

A total of 86 patients had been enrolled in the study, out of an expected total of 108, prior to Dr. Tan's release of preliminary results at a symposium that was sponsored by the American Society of Clinical Oncology.

Patients were stratified by polymorphisms in the thymidine synthase (TYMS) gene, which encodes for an enzyme that serves as a prime target for 5-fluorouracil (5-FU).

The more triple-repeat patterns identified in a certain region of the gene, the more likely a patient is to be resistant to 5-FU and to face a poor prognosis, Dr. Tan explained.

"If you can identify patients that will have a poor response to 5-FU-only chemoradiation, then the addition of another active agent may improve outcomes," he said.

A prospective study was therefore designed to selectively add the drug irinotecan to a neoadjuvant chemoradiation protocol in patients with a bad-risk TYMS genetic profile, also known as a triple-triple polymorphism.

All patients in the study also received the standard regimen used to treat Washington University patients with T3 and T4 adenocarcinoma of the rectum: 5-FU-based chemotherapy plus radiation, followed by restaging and resection 6-10 weeks following therapy.

Of the 86 patients, 63 were found to have good-risk genetic profiles. Previous research suggested that 60% of the good-risk patients would be expected to respond so well to the regimen that they could be downstaged at surgery.

Downstaging is associated not only with a better prognosis, but also with a better chance at sphincter preservation during surgery, Dr. Tan noted.

The predicted outlook was less optimistic for the remaining 23 patients.

Of the bad-risk patients, 12 of 17 (71%) were downstaged at surgery, far more than expected; 8 had a complete pathologic response to chemoradiation.

Previous research suggested just 22% of patients with a bad-risk genetic profile could be downstaged at surgery. Not all of the patients underwent surgery following chemoradiation, but of those who did, 30 of 52 patients (58%) with a good-risk genetic profile were downstaged, just as predicted.

Moreover, 12 of 17 (71%) of the bad-risk patients were downstaged at surgery, far more than expected. Eight of the patients showed a complete pathologic response to chemoradiation.

Among the five bad-risk patients who were not downstaged, four had surgical pathology specimens that showed only microscopic disease.

Of 17 bad-risk patients who were treated with irinotecan, 5-FU, and radiation, 16 "had a very good response to this strategy," Dr. Tan said at the symposium.

In addition to the American Society of Clinical Oncology, the symposium was co-sponsored by the American Gastroenterological Association, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology.

Grades 3 and 4 diarrhea were more prevalent among patients in the bad-risk group who were receiving irinotecan in addition to the standard chemoradiation regimen, he added.

One death occurred in both the bad- and good-risk groups.

Dr. Tan and his associates concluded that "genotype-directed therapies" are feasible for rectal cancer, and may offer significant advantages for patients with bad-risk genetic profiles. ■