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Genetic profile predicts which bladder cancer patients will benefit from early chemotherapy

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Three genetic changes can predict whether a patient will benefit from chemotherapy before surgery to remove bladder cancer, according to new findings presented by Fox Chase Cancer Center researchers during the 50th Annual Meeting of the American Society of Clinical Oncology.

During the study, 36 patients with muscle-invasive bladder cancer received chemotherapy before surgery, consisting of an accelerated regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC). By the time surgery rolled around, 14 patients appeared cancer-free. All but one of these patients carried mutations in at least one of three specific genes; none of these mutations were present in any of the people who still harbored traces of cancer after AMVAC.

These results suggest that doctors may one day sequence patients' tumors for the presence of these three mutations, to determine who will likely benefit most from chemotherapy before surgery, said Elizabeth R. Plimack, MD, Attending Physician in the Department Medical Oncology at Fox Chase.

"The purpose of the study is to find ways to identify patients who are likely to respond to early chemotherapy," said Dr. Plimack. "For those patients who won't benefit from it, we can send them directly to surgery to save time. But if they carry at least one of these mutations, we can treat them knowing they are likely to respond," she noted.

To uncover a genetic pattern that predicted responses to AMVAC, Dr.

Plimack and her colleagues in collaboration with Foundation Medicine sequenced 287 cancer-related genes in tissue samples taken before patients underwent chemotherapy. The analysis clearly landed on three genes, all associated with repairing damaged DNA, carried by all but one of the people who benefited from chemotherapy. To see such a clear distinction between the genetic profiles of responding and non-responding tumors is remarkable, Dr. Plimack added. "It is unusual to see statistics this good," she said.

Additionally, patients whose cancer disappeared after AMVAC tended to carry more mutations in their tumors than those with residual cancer at the time of surgery.

It makes sense that the three key genes are associated with DNA repair, said Dr. Plimack. Patients who carry these mutations will likely have more mutations because their cells cannot easily repair cellular damage, so when cancer starts, mutations quickly accumulate. But since cisplatin works by further damaging DNA, these same tumors are more likely to succumb to its effects, since they lack mechanisms to sidestep chemotherapy. "These patients may have developed cancer because a damaged cell couldn't repair itself, but once they have cancer, the defective DNA repair machinery makes the tumor more likely to respond to chemotherapy because the cells can't repair the additional damage caused by cisplatin," said Dr. Plimack.

The results point to a new way to screen patients to select those who will benefit most from cisplatin-based chemotherapy. Looking for these mutations involves a genomic sequencing test that's already commercially approved, and available to any clinician, said Dr. Plimack. But she cautioned that more work needs to be done, and she and her colleagues are now testing tissue samples from another set of patients to make sure the results hold up. "Although the statistics are exciting, and the mechanism makes sense, the results are preliminary. We do not

recommend treatment decisions be made based on this test until it is validated"

Provided by Fox Chase Cancer Center