New medications show promise in treating drug-resistant prostate cancer

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A new therapy for metastatic prostate cancer has shown considerable promise in early clinical trials involving patients whose disease has become resistant to current drugs.

Of 30 men who received low doses of one the drugs in a multisite phase I/II trial designed to evaluate safety, 22 showed a sustained decline in the level of prostate specific antigen (PSA) in their blood. Phase III clinical trials are planned to evaluate the drug's effect on survival in a large group of patients with metastatic prostate cancer.

The drugs are second-generation antiandrogen therapies that prevent male hormones from stimulating growth of prostate cancer cells. The new compounds - manufactured by the pharmaceutical company Medivation and known as MDV3100 and RD162 - appear to work well even in prostate cells that have a heightened sensitivity to hormones. That heightened sensitivity makes prostate cancer cells resistant to existing antiandrogen therapies.

The drugs were discovered in the laboratory of Howard Hughes Medical Institute investigator Charles Sawyers at Memorial Sloan-Kettering Cancer Center in collaboration with chemist Michael Jung at UCLA. He and his colleagues described the development of the drugs and initial testing in an article posted online April 9, 2009, in *Science* Express, which provides electronic publication of selected *Science* articles in advance of print. Sawyers's team collaborated on the studies with researchers from the University of California Los Angeles, Oregon

Health and Science University, University of Washington and Medivation.

About 186,000 new cases of prostate cancer are diagnosed each year in the United States. The male hormones testosterone and dihydrotestosterone -- also known as androgens -- spur the growth of prostate cells, and drugs that block the receptors for these hormones are the most common treatment for the disease in its advanced, metastatic stage. Antiandrogen drugs, such as bicalutamide, suppress the growth of cancer cells temporarily, but in most patients the cancer ultimately develops resistance to drugs. About 29,000 men in the United States die each year from the disease.

Prostate cancer becomes resistant to antiandrogen drugs when cancer cells begin to increase production of the androgen receptor, said Sawyers. When the level of androgen receptors on the cells' surface reaches a certain level, the drugs that originally suppressed the cancer actually begin to stimulate cancer growth.

Because of this backlash effect, many scientists have questioned whether blocking the androgen receptor is a wise course of action. But Sawyers and his colleagues believe that blocking the receptor is critical to successful treatment. So they set out to design a new generation of drugs that can block the androgen receptor without unwanted side effects, even when levels of the receptor are high.

Researchers in Sawyers' lab based their designs on a drug that tightly attaches to the site on the androgen receptor that binds testosterone. If that site is blocked, the hormone cannot bind to prostate cells and tell the receptor to stimulate growth. Using this molecule as a chemical scaffold, the researchers synthesized nearly 200 slightly different versions of the drug. They tested each one in the lab on prostate cancer cells that had been engineered to produce high levels of androgen receptor.

This screening yielded two molecules, RD162 and MDV3100, which tightly bind to the androgen receptor and did not show the cancer-stimulating effect of bicalutamide and other current antiandrogen drugs. The molecules were good candidates for drugs, because they are readily absorbed into the blood when taken orally and they persist in the bloodstream.

The researchers tested the new drugs' effectiveness in mice with tumors derived from drug-resistant prostate cancer cells. "To our delight, we found that these compounds caused very dramatic shrinkage of tumors in the mice," said Sawyers. "While treating these animals with bicalutamide produced a modest effect on their tumors, the new drugs caused the tumors to shrink dramatically, and in some animals almost completely," he said.

Sawyers said the new drugs bind tightly enough to the natural hormone-binding site on androgen receptors to prevent most of them from functioning - even in cells with a lot of androgen receptors. Bicalutamide interferes with the receptor through a different mechanism, which backfires, when too much androgen receptor is present, Sawyers explained.

The promising laboratory studies led Medivation to license the drugs for commercial development, said Sawyers, who serves as a consultant to the company and would receive royalties on the drug should it prove to be successful.

The company chose to use MDV3100 for clinical studies, which began in 2007. In those initial studies, 30 men with antiandrogen-resistant prostate cancer received low doses of MDV3100. Twenty-two of those men showed a sustained decline in their blood levels of prostate specific antigen (PSA), an indication that their cancer was responding favorably to the drug. This trial is still under way, and results from a total of 140

patients receiving higher doses of the drug will be reported within the next year, said Sawyers.

Medivation has received permission from the Food and Drug Administration for a large clinical trial of MDV3100 on about 1,200 patients with antiandrogen-resistant disease. This study will assess MDV3100's effect on cancer survival and will take several years.

While these preliminary results are promising, Sawyers said his laboratory will continue to seek further improvements in drug therapy for prostate cancer. "There were some men in the initial trial in which the drug didn't work at all, and we want to find out why," he said. "It may be because the drug is not potent enough to overcome resistance due to androgen receptor overexpression. Or, it may be that the cancers in these men are not driven by the androgen receptor anymore. Also, there were men who initially received benefit from the drug, but then relapsed, and their PSA levels came back up. We want to understand the mechanism of that relapse and to try to develop drugs that prevent that renewed resistance," he said.

Source: Howard Hughes Medical Institute