Antifungal drug delays need for chemo in advanced prostate cancer

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The oral antifungal drug itraconazole, most commonly used to treat nail fungus, may keep prostate cancer from worsening and delay the need for chemotherapy in men with advanced disease. Details of the finding, from a clinical trial led by Johns Hopkins experts, are scheduled for presentation on Saturday, June 4 at the 2011 American Society of Clinical Oncology (ASCO) annual meeting (abstract #4532).

Currently, the drug is approved to treat fungal infections in nails and other organs. Serious side effects can include heart failure, and Johns Hopkins experts caution that itraconazole needs further study before it can be considered for prostate cancer treatment.

Identified as a potential anticancer drug after Hopkins scientists scoured a database of more than 3,000 FDA-approved drugs, itraconazole appears to block tumor blood vessel growth -- the only drug in its class to do so -- much like the anticancer drug bevacizumab (Avastin). The antifungal also disrupts a key cancer-initiating biological pathway called Hedgehog. Laboratory testing by Johns Hopkins scientist Jun Liu, Ph.D., has shown that human prostate tumors implanted in mice shrink when treated with itraconazole.

"The most effective therapy we have right now for metastatic prostate cancer is hormone therapy, and when it doesn't work, the next step is usually chemotherapy," says Emmanuel Antonarakis, M.D., assistant professor of oncology at the Johns Hopkins Kimmel Cancer Center. In a search for compounds that could put off chemotherapy, the Johns

Hopkins team turned to itraconazole.

For the study, patients with prostate cancer that had spread to other organs and did not respond to hormone therapy were randomly assigned to receive low or high doses of itraconazole.

Over 24 weeks of daily treatment with oral itraconazole, the investigators tracked the length of time for each patient's prostate cancer to worsen (called progression-free survival). Evidence of worsening disease was measured by a 25 percent increase in their blood level of prostate specific antigen (PSA), a marker for prostate cancer.

Early in the trial, preliminary analysis of 17 men receiving low doses of itraconazole showed that only two of them (11.8 percent) had stable or declining PSA. Because of the limited response, no further men were given low doses of the drug.

However, 11 of 24 (48.4 percent) men taking high doses of itraconazole had stable or declining PSA levels lasting at least 24 weeks. In addition, nearly a third of men taking the high dose had PSA reductions of 30 percent or more. Metastatic prostate cancer patients receiving no treatment typically would worsen in eight to 12 weeks, according to Antonarakis.

The investigators also found that 12 of 14 men taking high doses of itraconazole had lower levels of circulating tumor cells present in their blood after therapy, compared with their baseline levels.

Seven patients experienced side effects, including low potassium, hypertension and fluid retention, but the problems were resolved with potassium replacement pills, anti-hypertension drugs, and diuretics.

"We also tested whether itraconazole acted as hormone therapy by

tracking levels of testosterone and DHEA (a testosterone derivative) in the blood, and we found no reductions of either testosterone or DHEA," says Antonarakis. "This finding shows that itraconazole is not just another hormone therapy, and has a unique mechanism of action."

Antonarakis and colleagues next plan to examine blood and skin samples taken from study participants specifically to look for levels of proteins linked to tumor blood vessel formation and the Hedgehog pathway.

"With these results, we believe that high-dose itraconazole is worth studying in a larger group of men with advanced prostate cancer," adds Antonarakis.

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