Dutasteride May Reduce Prostate Cancer Risk

BY FRAN LOWRY
Orlando Bureau

ORLANDO — The investigational 5-α-reductase inhibitor dutasteride induces genetic changes in noncancerous prostate tissue and may play a role in reducing the risk of prostate cancer, Dr. Elahe Mostaghel said at a symposium on prostate cancer sponsored by the American Society of Clinical Oncology.

Dutasteride, which is currently used to treat benign prostatic hyperplasia, reduced the activity of 98 genes—including trefoil factor 3 (TFF3), whose overexpression has been associated with the development of prostate and other cancers—by more than twofold, said Dr. Mostaghel of the Fred Hutchinson Cancer Research Center, Seattle.

The 5-α-reductase inhibitors curb the conversion of testosterone to dihydrotestosterone (DHT) inside the prostate, decreasing DHT levels and thereby inhibiting cancer development. In the Prostate Cancer Prevention Trial, inhibition with the 5-α-reductase inhibitor finasteride resulted in a 25% reduction in the overall incidence of prostate cancer, but this finding was accompanied by an unexpected increase in the number of high-grade prostate cancers in the men who did get cancer.

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"The results from the [Prostate Cancer Prevention] trial are what have really prevented this chemoprevention idea from becoming more widespread, because we really don't understand yet why there was an increase in the number of higher-grade tumors. It appears to be an artifact in the way the study was performed, the way the biopsies were done, and the way that the prostate-specific antigen thresholds were adjusted," Dr. Mostaghel said at the symposium, cosponsored by the Society of Urologic Oncology and the American Society for Therapeutic Radiology and Oncology.

In the present study, the researchers wanted to determine what was actually going on at the molecular level to decrease the development of prostatic tumors. Accordingly, Dr. Mostaghel and her coinvestigators examined gene expression changes in benign prostate epithelium from 75 men diagnosed with localized prostate cancer.

The men were randomized to prostatectomy alone (n = 25) or neoadjuvant dutasteride at 0.5 mg (n = 26) or 3.5 mg (n = 24) orally per day for 4 months prior to prostatectomy.

Dihydrotestosterone levels fell by 93% in the men treated with 0.5 mg dutasteride, and by 98% in the 3.5-mg-per-day group. Treatment with dutasteride induced upregulation of 32 genes and downregulated 98 genes, including several genes potentially involved in prostate cancer development. Among them were:

▶ **Insulinlike growth factor–binding protein 3 (IGFBP3).** This gene was upregulated in response to dutasteride. It promotes apoptosis and inhibits cell proliferation and is decreased in patients with prostate cancer.

▶ **Transmembrane protease, serine 2 (TMPRSS2).** This gene was downregulated in response to dutasteride. It is an androgen-regulated gene that is thought to promote the development of prostate tumors when it fuses with other oncogenes, such as ETS. TMPRSS2-ETS fusions have been found in up to 70% of prostate cancers.

▶ **TFF3.** This gene inhibits apoptosis and promotes tumor aggression. It is also overexpressed in gastrointestinal and breast cancers, in addition to prostate cancer.

Dutasteride is being evaluated in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which will be completed in 2009, Dr. Mostaghel said.

"We need to wait for the results of the REDUCE trial," he said. "In our exploratory study, we demonstrated a mechanism by which dutasteride may reduce the risk of prostate cancer. REDUCE will tell us whether the gene expression changes we are seeing with dutasteride will correlate with developing or not developing prostate cancer, so our findings need validation in larger studies of longer duration." ■