Guideline Summary

Use of 5- α -Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline Summary

In 2005, the ASCO Health Services and Prevention Committees and the American Urological Association jointly convened an expert panel to make recommendations regarding the chemoprevention of prostate cancer and recommendations concerning the use of 5- α -reductase inhibitors (5-ARIs). The guideline¹ published in *Journal of Clinical Oncology* was developed on the basis of a systematic review by Wilt et al,² which included nine randomized controlled trials reporting prostate cancer period prevalence.

Clinical Questions

In developing the guideline, the panel asked the following clinical questions about existing evidence regarding 5-ARIs and prostate cancer: How do 5-ARIs affect the risk of incident prostate cancer, prostate cancer mortality, and overall mortality? How do they affect benign prostatic hyperplasia (BPH) and quality of life? What are the benefits and harms of using 5-ARIs for prostate cancer prevention? What are their effects on development of different grades or stages of prostate cancer? What should physicians consider in assisting men in shared decision making?

Evidence

The panel drew on evidence from nine randomized clinical trials,² in which men who were receiving regular prostate-specific antigens (PSAs) and digital rectal examinations (DREs) were administered a 5-ARI for 1 to 7 years, as well as shorter studies of 5-ARIs as treatment for BPH.² The trial

results were mostly consistent. The largest trial was the Prostate Cancer Prevention Trial (PCPT),³ with 18,882 patients of the total 33,403 who participated in trials lasting longer than 1 year. To our knowledge, the PCPT is the only reported trial designed to test the efficacy of a 5-ARI (finasteride) in preventing prostate cancer. It is also the most reliable trial for directly comparing the benefits and harms of finasteride in the most likely target population for interventions to prevent prostate cancer. The men in the PCPT had normal DRE results and PSA less than 3 ng/mL at study entry.

In the trials studied by the panel, 5-ARIs decreased the proportion of participants diagnosed with prostate cancer during the trial period of for-cause prostate cancer by approximately 26%, with a similar decline in relative risk of any prostate cancer (compared with placebo). The absolute risk reduction in period prevalence of for-cause prostate cancers was 1.4%. On the basis of the PCPT,³ 71 men would have to be treated with a 5-ARI for 7 years to prevent one case of prostate cancer. By comparison, 100 women (with 2% baseline risk of breast cancer) would have to be treated for 6 years with tamoxifen to prevent one case of breast cancer.¹

The trials were not powered to show differences in mortality, and they did not find such differences. Nevertheless, the panel concluded that even if 5-ARI treatment never translated into reduced overall or prostate cancer-specific mortality, the reduction in risk of prostate cancer diagnosis, with the consequent morbidity of treatment, was a clinically beneficial end point in and of itself.

Recommendation

Asymptomatic men with a prostate-specific antigen (PSA) $\leq$ 3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of the benefits of 5- α -reductase inhibitors (5-ARIs) for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer) to be able to make a better-informed decision. Men who are taking 5-ARIs for benign conditions such as lower urinary tract (obstructive) symptoms would benefit from a similar discussion.

The first analysis of the PCPT³ showed a statistically significant decrease in period prevalence, and the panel accepted this finding. One panel member felt the difference in period prevalence was a result of different biopsy rates in the two trial arms. However, the primary investigator of the PCPT disagreed. Whereas the large majority of the panel felt that the benefit of the decrease in period prevalence was clear, a secondary analysis showed an increase of high-Gleason score (grade 8 to 10) prostate cancer in the treatment arm. The PCPT investigators, practicing physicians, and panel members all struggled with the question of whether the increase in high-grade cancers reflected a real risk in use of finasteride or whether this was a result of confounding factors.

After reviewing additional analyses of the data, which tested hypotheses about various explanations, the panel judged that plausible reasons could have led to a nonauthentic increase in high-grade cancers. The panel concluded that a true finasteride-mediated initiation or promotion of high-grade tumors could not explain both the increase in incidence of high-grade prostate cancer in the finasteride arm of the PCPT and the simultaneous decrease in incidence of lower-grade tumors.

It is important to note that there is no information on the long-term outcomes for a given histologic grade in men who have received a 5-ARI compared with men who have not received a 5-ARI. Until there is, decisions regarding treatment intervention should be made on the basis of histologic information obtained on biopsy, regardless of 5-ARI status.

Many men receive 5-ARIs for benign conditions, such as lower urinary tract (obstructive) symptoms, BPH, or male pattern baldness. These men may benefit from a discussion about the observed increase in high-grade prostate cancers in men receiving finasteride in the PCPT³ and the theoretic possibility of increased risk of prostate cancer mortality. Because the increase likely resulted from an artifact, the observed benefits in improvement of symptoms in these conditions should be weighed with the potential risks of high-grade prostate cancer as a result of 5-ARI use.

Additional Benefits and Harms

Studies and meta-analyses have demonstrated a reduction in risk in acute urinary retention with use of 5-ARIs (from 5.6% to 3.3%; absolute risk difference, 2.3%) as well as a reduction in the need for surgical intervention (from 3.3% to 1.7%; absolute risk difference, 1.6%). The largest benefits were observed in men with baseline PSA > 4 ng/mL (ie, larger prostates).

Potential adverse effects were of small absolute size. There was a 2% to 4% increase in erectile dysfunction and gynecomastia, a 1% to 3% decrease in ejaculate volume, and a 1% to 4% decrease in libido. The sexual adverse effects decreased with time.

In the PCPT,³ the participants' PSAs were lowered by approximately 50% after 12 months. It is important to consider this when judging the clinical significance of a PSA value.

Duration of 5-ARI Use

The optimal duration of 5-ARI use in relatively healthy men with no prostate cancer and at average risk for developing it is unknown. In the PCPT,³ finasteride was administered for 7 years. Therefore, until additional information is available, it should be administered for 7 years if used in this setting. In an ongoing trial⁴ of dutasteride, the duration is 4 years. More

about the effects of the 4-year duration will likely be known at trial completion.

Applicability of Guideline Recommendations

It is important to note that all the men in the PCPT³ were receiving regular screening for prostate cancer. The impact of 5-ARIs, including finasteride, on the risk of development of prostate cancer in men who are not being actively screened is therefore not known. The PCPT study population included men > age 50 years who had normal DREs and PSAs. Furthermore, approximately 92% of the men in the PCPT were non-Hispanic whites.

Future Avenues of Research

The panel also looked at future directions of research regarding 5-ARIs for prostate cancer prevention. Additional research is needed to:

- Establish the effect of 5-ARIs on prostate cancer morbidity and mortality
- Establish the optimal dose of finasteride: 1 mg versus 5 mg
- Find a range of appropriate PSA cut points for men taking 5-ARIs to trigger biopsy (because 5-ARIs lower PSA approximately 50% within 1 year)
- Understand the role of 5-ARIs in men not receiving screening
- Establish the most effective means of communicating with men considering use of 5-ARIs or already taking them for other indications
- Provide risk stratification models incorporating molecular data

Definitions

- 5- α -reductase: Enzyme that converts testosterone into the more potent dihydrotestosterone. Dihydrotestosterone has two isoenzymes (isoforms), types 1 and 2. Finasteride inhibits type 2 isoenzyme, whereas dutasteride inhibits both types 1 and 2 isoenzymes
- Chemoprevention: Use of chemical compounds to reduce risk of development of a specific disease (here, specifically for reduction of risk of prostate cancer development)
- Period prevalence: Proportion of randomly selected population identified as having prostate cancer during trial period
- For-cause cancers: Those cancers found by—
 - Clinical suspicion during trial and confirmed on biopsy
 - End-of-study biopsy, when biopsy was recommended but not performed during trial
 - End-of-study biopsy with prostate-specific antigen > 4 or suspicious digital rectal examination

Physician-Patient Communication

- The physician should present available evidence and highlight the remaining uncertainties:
 - What is known about period prevalence
 - What is not known about high-grade cancer and mortality
 - What has yet to be resolved about the high-grade cancer question
- The physician should communicate that the risk of developing prostate cancer does not decrease to zero with use of 5-ARIs
- The physician and patient should discuss risks and benefits
 - Explain that sexual adverse effects seem to be reversible in most men
- The physician should emphasize that clinical trial results to date reflect 5-ARI use for 7 years, no longer
- A prostate cancer risk calculator is available online at <http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>, applicable to men:
 - Who are > 50 years of age
 - Who have not had prostate cancer
 - Who have prostate-specific antigen and digital rectal examination results from the past year

Results of ongoing studies of prostate cancer screening and mortality and results of the dutasteride study⁴ may help to answer some of these questions.

Guideline Resources

In addition to the full-text version of this guideline published in *JCO*,¹ ASCO provides a discussion guide (Data Supplement, online only) designed to enhance communication between physicians and patients, along with a slide set (Data Supplement, online only), also available at www.asco.org/guidelines/5ari.

Authors

The ASCO/American Urological Association clinical practice guideline for 2008 on use of 5-ARIs for prostate cancer chemoprevention was developed and written by Barnett S. Kramer, MD, MPH, Karen L. Hagerty, MD, Stewart Justman, PhD, Mark R. Somerfield, PhD, Peter C. Albertsen, MD, William J. Blot, PhD, H. Ballentine Carter, MD, Joseph P. Costantino, PhD, Jonathan I. Epstein, MD, Paul Godley, MD, PhD, Russell P. Harris, MD, Timothy J. Wilt, MD, MPH, Janet Wittes, PhD, Robin Zon, MD, and Paul Schellhammer, MD.

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