to assign newly randomized patients either to placebo or the arm generating the most positive results, thus maximizing the chance for an overall positive outcome. “Bias can be introduced by knowing the results associated with various choices of endpoints, subject subsets, or analyses, and choosing the most favorable,” the guidance warned.

In addition, if patients know the pre-specified point when the interim analysis would take place, they might delay enrolling in the trial until their chances of getting the more successful treatment increased. And “how should patients receiving the other treatment feel?” asked Buyce. “Should they drop out of the trial?”

Such concerns have limited the method’s deployment in confirmatory trials. According to Lee, a 2008 survey had identified just 50 clinical trials that used some form of adaptive clinical trial design. A more recent analysis, he said, came up with 72 trials with planned interim analyses. Fifty-six were stopped early with futility being the reason 70 percent of the time. The FDA could not name a single drug whose approval was based on a trial where patient assignment was changed mid-stream. “Success depends on finding good biomarkers to guide patients to assignment to better treatments,” Lee said. “Unfortunately we don’t have good markers or good treatments.”

Researchers who work closely with industry on new drugs seeking regulatory approval recognize the pitfalls of tampering with the original protocol in a confirmatory trial. “Going down in number is generally not advised,” said William Sietsema, Ph.D., vice president for global regulatory strategy at Cincinnati-based INC Research, Inc., a contract research organization that conducts numerous clinical trials for industrial clients. “You could end up with a trial without enough patients. Most companies would not shrink a trial size as the result of an interim analysis. They might make it bigger, or they might stop it, but they wouldn’t shrink it,” he said.

He also cautioned against “play the winner” designs that increase the number of patients being randomized to arms that show the best results in an interim analysis. “That is most often used in early phase trials, like a Phase I or early Phase II trial where you’re really trying to identify the best dose level; such trials tolerate bias pretty well,” Sietsema said. “But you wouldn’t use a play-the-winner model in a Phase III trial because the potential for bias could lead to a wrong decision and the FDA would object.”

Yet adaptive designs remain rare for early stage trials, too, even though regulators might have fewer objections and investigators could gain valuable experience in managing the process. “It’s paradoxical that adaptive design is not being used more in Phase I trials where it’s very useful,” Buyce told the ASCO forum, “and it’s not very much used in Phase III trials, which is where all the excitement is.”

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Urology Meeting Highlights Prostate, Bladder Cancers

By Mike Fillon

The United States Preventive Services Task Force (USPSTF) did not back off its controversial recommendations against PSA-based screening for all men, regardless of age, at the American Urological Association (AUA) Annual Meeting in Atlanta in late May. If anything, it dug its heels in.

Reaction came fast and loud from urology organizations, patient advocacy groups and AUA meeting attendees, starting with AUA president Sushil I. Lacy, M.D. “The AUA is outraged at the USPSTF’s failure to amend its recommendations on prostate cancer testing against prostate cancer risk.”

In October 2011, the USPSTF said its research found that routine PSA-based screening resulted in little or no reduction in prostate cancer-specific mortality and could cause unnecessary harms from evaluation and treatments. The Task Force is made up of 16 experts in prevention and evidence based medicine including cancer researchers. There weren’t any urologists on the Task Force. Their recommendation was based solely on a systematic review of available published evidence including clinical trials and a review of public comments.

Despite the objections at AUA, the USPSTF did not change its position. “Many people who commented on the
recommendations urged the Task Force to change the recommendation to a grade ‘C,’ meaning physicians could provide the test to patients who request it. But new evidence was not presented. “The recommendation remains unchanged,” the USPSTF said in a statement.

While certainly not scientific, a show of hands by audience members overwhelmingly opposed the USPSTF stance. Later in the day, speakers unanimously condemned the USPTF’s position at a news conference. “I think we would all agree that the appropriate use of PSA and DRE, combined with informed consent, especially in at-risk populations, does indeed reduce deaths from prostate cancer,” said John Lynch, M.D., a member of the AUA Board of Directors and a prostate cancer survivor. “It is a disservice to men to deny them the opportunity for potential treatment and cure, when necessary, for a disease that affects one in six over the course of their lifetime.”

“We are deeply disturbed that the Task Force failed to amend their recommendations to more appropriately address the use of the PSA test,” added David Penson, M.D., also representing the AUA. “The AUA, along with other major medical groups... believes that men should talk to their doctors about their individual prostate cancer risk, and that PSA testing is an individualized decision that should happen in the context of that discussion.”

**Bladder Cancer Guidelines Not Being Followed**

Prostate cancer screening wasn’t the only controversial issue at AUA. Karim Chamie, M.D., of the Department of Urology at the University of California, Los Angeles, pointed out that unlike improvement in outcomes for prostate and kidney cancers, the 5-year survival rate for bladder cancer since the 1980s has only improved 1%—from 79% to 80%. Chamie said the lack of improvement in survival is at least in part due to patients receiving less aggressive treatments than those with prostate and kidney cancer due to a lack of guidelines adherence.

“It is a disservice to men to deny them the opportunity for potential treatment and cure, when necessary, for a disease that affects one in six over the course of their lifetime.”

Chamie said that using the SEER (Surveillance, Epidemiology and End Results) registry, researchers identified every Medicare beneficiary in the registry diagnosed with bladder cancer. “Using that data we found that out of over 4,500 patients, only 1 patient received comprehensive guideline recommended care according to the AUA, European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) for high grade non-muscle invasive bladder cancer,” he said. “Unfortunately...it’s not the first time that anybody has demonstrated that bladder cancer patients are not getting the appropriate care.”

Surveillance and treatment measures for patients with high grade non-muscle invasive bladder cancer are typically outpatient procedures—that is, a protocol of cystoscopy, cytology, upper tract imaging and instillation of intravesical therapy—lies within the realm of most practicing urologists.

**Methylation in Cancer Detection**

Also at the conference, Peter Jones, Ph.D., discussed the promise of methylation research for cancer detection in a lecture entitled “Targeting Cancer Epigenome for Therapy.” As Jones pointed out, it’s not genes that influence cancer incidence, detection and therapy, but how those genes are packaged. When tumor suppressor or immune stimulator genes are methylated that package is locked, which can lead to neoplasia and cancer, Jones explained. “The potential for unlocking these genes is an exciting area of cancer research today, from locating markers that detect methylation to developing drugs to demethylate those genes,” he said.

Jones, who is a professor of urology, molecular biology and biochemistry at the University of Southern California, said that when genes are locked off by DNA methylation they aren’t mutant and haven’t been lost, and it is possible to put them back into action. Furthermore, methylation changes could be detected in urine and blood with a very high degree of specificity and sensitivity, which is one reason to study them. “The current interest, though, is in the area of epigenetic therapy, where the idea is to turn on genes which were locked off by methylation,” he said.

Another promising area of research that involves removing the methyl groups from the relevant genes is combining epigenetic therapy and immunotherapy.