EDITORIAL USPSTF and FDA: PSA and 5ARIs

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It has been a tumultuous season. The urology world has been rocked by two far-reaching, authoritative and independent rulings by American policy makers. First, the United States Preventive Services Task Force (USPSTF) published a new recommendation about prostate-specific antigen (PSA) screening.[1] It relegated it to a level "D" recommendation. Second, the Food and Drug Administration (FDA) ruled against the use of 5-alpha reductase inhibitors (ARIs) for prostate cancer prevention, largely due to concerns about an increase in high-grade cancer.[2]

Both of these rulings have created uncertainty on the part of physicians and patients. In my opinion, both were predictable in the frame of reference of the two organizations, both were flawed and both need to be reinterpreted in the Canadian context.

The USPSTF ruling on PSA testing

The draft recommendation includes misinformation and errors of omission. The Task Force did not acknowledge that screening certain patient groups, such as younger and healthier patients, reduces prostate cancer (PC) death rates. The positive higher quality trials (ERSPC and Göteborg studies) were dismissed for not showing an overall survival benefit; but the primary endpoint of these randomized controlled trials (RCTs) was PC-specific mortality, not all-cause mortality; this should not be a point of criticism. Data from the flawed PLCO trial should not have been combined in meta-analyses with data from the ERSPC and Goteborg trials, which showed 20% and 44% reductions in PC mortality, respectively. The task force did not acknowledge the dramatic 44% mortality benefit in the healthy patient subset within the PLCO, with a number needed to treat (NNT) of 5 as reported by Crawford.[3] The Task Force did not consider the 40% reduction in prostate cancer mortality that has occurred since the advent of PSA testing.

However, the major criticism of the Task Force was that PSA screening results in over-diagnosis and overtreatment. This hits home. With the most recent CaPSURE data showing that more than 90% of the most favourable-risk patients (CAPRA 0-2) are still treated radically in the U.S. our American colleagues had it coming, Canada appears to be different in this regard. Active surveillance for favourable-risk disease has been widely embraced in this country. This fundamentally alters the NNT equation and makes PSA-based early detection far more palatable. Clearly, the USPSTF position risks throwing the baby out with the bathwater. The Canadian policy towards PSA testing should be much more positive, given that the overtreatment problem has been addressed to a significant degree by selective therapy.

The FDA position on 5 ARIs

The FDA position followed an Oncology Drug Advisory Committee (ODAC) panel last December. The ODAC panel advised that the 5-ARIs do not have a favourable risk benefit profile for chemoprevention of prostate cancer in healthy men. Importantly, this was in the context of the "real world," i.e., concerns that a favorable ruling would likely result in men taking the drug without proper evaluation or follow-up. The FDA acknowledged that 5-ARIs reduce the likelihood of prostate cancer diagnosis substantially. Importantly, the FDA did not alter the policy regarding the benefit of the drugs for BPH/LUTS, but emphasized that patients must be informed about the small high-grade cancer risk (about 1 case per 200 patients).

This policy also is at variance with the Canadian situation, where men taking 5-ARIs are, in most cases, followed by urologists or concerned primary care physicians. On November 20, 2011 in Toronto, a consensus conference was held involving Canadian prostate cancer and BPH experts. Participants addressed the role of 5-ARIs in the wake of the FDA decision. We expect this will result in a patient brochure for men on the

drugs, and a guideline for Canadian physicians. The consensus will be published in an upcoming issue of *CUAJ*.

Thinking through both rulings

Finally, there is a link between these two rulings by independent policy groups that is important to note. The benefit of 5-ARIs is largely in the reduction of Gleason 6 prostate cancer. These cancers are a problem primarily in screened populations. If the USPSTF ruling is accepted as such, and PSA testing fades away, it is likely that Gleason 6 prostate cancer (which is rarely, if ever, fatal, and largely a screen diagnosed entity) will be increasingly rare, and the value of preventing these cancers will disappear.

Thus, the position that there is a role for 5-ARIs in prevention, insofar as it implies ongoing screening, runs counter both to the FDA position and (by implication) to the USPSTF position. For those who believe that both of these positions are flawed, this poses a challenge. One must defend a stance against two American regulatory bodies, which both claim to be dispassionate. As urologists, we are viewed by skeptics as members of an interest group with a conflict of interest, whose practices and pocketbooks benefit from the dramatic increase in prostate cancer cases associated with PSA testing. The challenge is to make the case (which I believe is valid) that PSA screening (properly managed) and 5 ARIs (used judiciously) benefit patients, without being dismissed as another self-serving interest group. It makes for interesting times.

References

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