EDITORIAL

Prostate Cancer Chemoprevention: More than Meets the Eye

Three large evidence based clinical trials focused on prostate cancer have been completed with several more in process to investigate strategies to prevent prostate cancer. While the SELECT trial that used vitamin E and selenium alone and in combination did not prove successful, two other large clinical trials have now demonstrated that the use of a 5 alpha reductase inhibitor (5 ARI) can reduce the future risk of prostate cancer diagnosis. The PCPT (Prostate Cancer Prevention Trial), initially published in 2003, used finasteride as the 5 ARI and reduced the relative risk of prostate cancer by about 25% over 7 years in men with a PSA of less than 3 ng/mL. More recently, the REDUCE trial used the 5 ARI dutasteride in a group of higher risk men (i.e. recent negative prostate biopsy, PSA levels 2.5-10 ng/mL) and demonstrated a 23% relative risk reduction in biopsy detected prostate cancer.

While designed as "chemoprevention trials", multiple published follow up analyses of the PCPT data and pending publications from the REDUCE study population have provided many important insights in our understanding of prostate cancer beyond their stated purpose. The PCPT forever changed our understanding what a "normal" PSA is as many men with a PSA < 4.0 ng/mL (including levels < 1.0 ng/mL) had prostate cancer on study mandated biopsies. The use of finasteride improved the utility of the digital rectal exam and PSA determination in the detection of prostate cancers. Data presented at national meetings has shown the same enhanced utility of PSA to detect prostate cancer in men on dutasteride, and in particular, detect higher grade disease. The notion that the failure of PSA to reduce by 50% after 6 months of a 5 ARI is suggestive of prostate cancer seems to be of little value based on these studies. Nomograms have been constructed to determine the risk of a positive biopsy based on multiple parameters courtesy of the PCPT data.

Challenges remain in this area. Could these strategies have been used in some men with pre-existing/undiagnosed prostate cancer and in fact not be preventative? Are we doing prostate cancer "chemoprevention" or prostate cancer "risk reduction" by decreasing the likelihood of being diagnosed with a cancer in the future through PSA suppression? There is still lingering concern over the increased diagnosis of higher Gleason grade prostate cancer in some men on 5 ARI in these studies. Many papers suggest that this is purely a biopsy sampling artifact. Consider that 5 ARI might clear non-life threatening lower Gleason grade cancers (i.e Gleason grade 6) and allow the subsequent detection and treatment of those cancers that need an aggressive approach, a positive aspect. How do we ensure that our primary care colleagues and patients recognize that the simple reduction in serum PSA induced by 5 ARI is not assurance that cancer is not present and that the changes in PSA take on more meaning in this setting? We must continue to work to clearly identify those individuals who will gain the most benefit from these chemoprevention strategies.

All clinical trials and their findings must be fairly reviewed and critiqued, the core principle of our peer review process. However, we must not let potential downsides of these trials overshadow the tremendous benefits that they bring to our understanding of this very common and very challenging disease. While the SELECT trial using the vitamins and micronutrients approach did not meet its goal, the PCPT and REDUCE confirmed that 5 ARI's can reduce the incidence of biopsy detectable prostate cancer.

Congratulations to our colleagues and our patients for contributing over 62,000 participants to these three important, and prostate centric, large scale trials. While we continue the search for other agents and potentially modifiable risk factors, the 5 ARI's finasteride and dutasteride remain the only proven agents in this area.

The buzz word today is "evidence based medicine". Prostate cancer chemoprevention trials have provided us with much more than just evidence based data on ways to reduce the risk of prostate cancer and they will continue to do so for many years to come.

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