

New Studies Presented at the ASCO and AUA Annual Meetings

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Scientific meetings are built around the presentation of results from new studies. For example, in the last issue of PCRI Insights I summarized the findings from several new studies presented at the February Genitourinary meeting of the American Society of Clinical Oncology (ASCO). Since that time, in May and June, two even larger medical meetings have occurred: the annual meeting of the American Urological Association, the AUA, and another, larger ASCO meeting. I have selected some reports from these two meetings and comment on them in this article

Xtandi for Hormone Sensitive Disease and as a Primary Treatment Option for PCa

Over the years at Prostate Oncology Specialists where I work, we have championed the use of testosterone inactivating pharmaceuticals (TIP)—also known as hormone therapy or ADT—as a primary treatment alternative to surgery or radiation. Ten years ago, when severe radiation side effects were common, TIP was preferable to radiation because TIP had fewer side effects. However, as radiation technology has improved, we have been relying less and less on TIP.

However, Xtandi, a potent new type of TIP, may cause us to consider hormone therapy as an equally viable and effective primary treatment option. Even though Xtandi was FDA approved for treating advanced hormone-refractory prostate cancer, there is reason to believe it can be effective in the earlier stages of the disease. It's quite conceivable that Xtandi will be a more effectual treatment than the traditional LHRH agonists such as Lupron, Trelstar, Eligard and Zoladex, while causing less post-treatment side effects.

Abstract 5001

Dr. Smith and colleagues administered Xtandi 160 mg daily for 25 weeks to 67 men who had no previous TIP. The side effects reported were breast enlargement and fatigue in about a third of the men and hot flashes in one-fifth. Effects on libido and potency were not reported. Mean decrease in PSA was 99.6%. Testosterone and estrogen levels increased 114% and 72% respectively. Bone density and fat body mass were not substantially impacted.

◆**Comment:** Xtandi seems like the logical choice for men interested in TIP as a primary form of therapy because it “blocks” testosterone activity rather than completely shutting it down (as do the LHRH agonists). As such, the recovery period when the treatment is over should be much shorter. At Prostate Oncology Specialists we are presently investigating the use of six months of Xtandi with Femara (to prevent breast growth) in men with Intermediate-Risk Disease.

Aspirin, Metformin, Sulforaphane (Broccoli), Polyphenols and Vitamin D for PCa

Prostate cancer tends to be a slow-growing disease. Survival, even after relapse from surgery or radiation, is similar to men who don't have prostate cancer. Even so, many who relapse require intermittent therapy with TIP to control the disease. After a period of years, some men can become refractory to TIP and some of these who are refractory will have their lives shortened by the disease. Agents that can further impede

the already slow growth rates of prostate cancer have the potential to significantly improve survival (for example, if a hypothetical cancer is doubling at a rate of every six months and could be slowed down to a doubling rate of every nine months, life expectancy could be prolonged 50%). A number of supplements have shown cancer inhibitory qualities. Several reports presented at the cancer meeting confirmed their effects on PCa.

Abstract 5084, Aspirin

Cyclooxygenase-2 (COX-2) expression in prostate cancer has been associated with high-grade tumors and poorer prognosis. Use of aspirin, a COX-1 & 2 inhibitor, have been associated with reduced prostate cancer mortality in some studies.

◆**Methods:** National Cancer Registry Ireland data was used to identify men with stage I-III prostate cancer, diagnosed from 2001-2006. Aspirin use in the year preceding prostate cancer diagnosis was identified. Cox proportional hazards models, adjusted for age, smoking status, year of incidence, comorbidity score, Gleason score, tumor size, pre-diagnostic statin use, and receipt of radiation (time varying) were used to estimate hazard ratios (HR) for associations between aspirin use and all-cause and prostate cancer-specific mortality.

◆**Results:** 2,936 men were identified. Median follow-up was 5.5 years. Aspirin use was associated with a significantly lower risk of prostate cancer-specific mortality in men receiving >75mg of aspirin. Stronger associations were observed in men with higher aspirin dosing or a Gleason score >7.

◆**Conclusions:** Pre-diagnostic aspirin use was associated with a significant reduction in prostate cancer-specific mortality in men receiving >75mg of aspirin.

◆**Comment:** We know that aspirin 81 mg daily cuts

the risk of coronary events in men by one-third. Typically, side effects, mainly gastric upset or ulcers are rare. One of the good things about aspirin is that it is a blood thinner. Other blood thinners (such as Coumadin) have been shown to prolong prostate cancer survival (see the article I wrote in the last issue of Insights). This new report on aspirin supplies further evidence that daily aspirin should be considered routine in men with prostate cancer.

Abstract 5007, Metformin

Data were obtained from several Ontario health care administrative databases

◆**Results:** The cohort consisted of 3,837 patients. Cumulative duration of metformin treatment, after prostate cancer diagnosis, was associated with a significant decreased risk of prostate cancer-specific and all-cause mortality in a dose-dependent fashion. The adjusted hazard ratio, for prostate cancer-specific mortality was 0.76 for each additional six months of metformin use. The association with all-cause mortality was also significant but declined over-time from a HR of 0.76 in the first 6 months to 0.93 between 24-30 months.

◆**Conclusions:** Increased cumulative duration of metformin exposure after prostate cancer diagnosis was associated with decreases in both all-cause and prostate-cancer-specific mortality among diabetic men.

◆**Comment:** This report substantiates other previously published studies on the anticancer effects of metformin (otherwise known as Glucophage). Like vegetarian and macrobiotic diets, metformin lowers insulin levels. Insulin, which is like a type of growth hormone, has been implicated as a causative agent that accelerates cancer growth. In my book, *Invasion of the Prostate Snatchers*, a whole chapter was devoted to the important topic of how insulin affects prostate cancer.

Abstract 5017--Sulforaphane

Patients with PSA recurrence were treated with 200 μ mol of sulforaphane extract for up to 20 weeks.

◆**Results:** Sixteen patients completed 20 weeks of treatment. One patient experienced a PSA decline >50%. Thirty-five percent of patients had lesser PSA declines (3% to 20%), and 15% of patients had a final PSA lower than baseline. There was a significant reduction in PSA doubling time (6 months pre-study vs. 9.4 months on-study, $p=.013$). One patient discontinued study treatment for grade one GI discomfort.

◆**Conclusions:** This study provides a preliminary observation of improved PSA modulation with sulforaphane in men with prostate cancer.

◆**Comment:** Sulforaphane is thought to be the active ingredient in broccoli. Sulforaphane increases the intracellular concentration of an important anti-oxidant enzyme called glutathione transferase, which is abnormally suppressed in prostate cancer cells. This small study provides further evidence for the possible anticancer effects of sulforaphane.

Abstract 5008, Polyphenol-rich food

Foods such as pomegranate, green tea, broccoli and turmeric have anti-neoplastic effects in cell lines and animal models.

◆**Methods:** 203 men with localized prostate cancer after PSA relapse were randomized to receive an oral capsule containing a blend of pomegranate seed, green tea, broccoli and turmeric or placebo for 6 months.

◆**Results:** The median rise in PSA was 14.7% versus 78.5% with Placebo, $p=0.0008$. 46% of men had stable or lower PSA at trial completion versus 14% in the men treated with placebo. Mild gastro-intestinal issues were the only side effects.

◆**Conclusions:** This study found a short-term favorable effect on the percentage rise in PSA.

◆**Comment:** All these substances; pomegranate, green tea, broccoli and turmeric (curcumin) have been previously implicated as having inhibitory effects on cancer growth. In this study all four substances combined had a fairly dramatic effect on PSA progression.

Abstract 5036, Vitamin D

Emerging evidence in the literature suggests a positive association between serum 25-hydroxyvitamin D and survival in certain types of cancer.

◆**Methods:** A case series of 54 newly diagnosed stage IV prostate cancer patients underwent vitamin D evaluation prior to receiving treatment. We defined vitamin D insufficiency as serum 25(OH)D levels of ≤ 32 ng/ml. Cox regression was used to evaluate the prognostic significance of vitamin D on survival after adjusting for age, PSA and functional status.

◆**Results:** Mean survival was 32.6 months and 62.4 months for patients in ≤ 32 ng/ml and >32 ng/ml groups respectively ($p = 0.02$). On multivariate analysis controlling for age, performance status and PSA, patients with levels >32 ng/ml demonstrated significantly lower mortality (HR=0.13; $p=0.05$) compared to those with levels ≤ 32 ng/ml.

◆**Conclusions:** Higher circulating levels of Vitamin D were positively associated with survival in patients with metastatic prostate cancer.

◆**Comment:** All the agents listed in this section; Aspirin, Vitamin D, Curcumin, Sulforaphane, pomegranate and green tea have shown potential anti-cancer effects. Generally, these agents cause little to no side effects. Their usage in men with prostate cancer, along with diet and exercise, is considered routine in our medical practice at Prostate Oncology



Specialists.

The Danger of Mindless Prostate Biopsy

For several years I have been cautioning about the overuse of random prostate biopsy. My main concern is the over diagnosis of a small, slow growing, innocuous prostate cancer, the diagnosis of which frightens men into unnecessary radical treatment. In addition, the biopsy procedure itself can have direct deleterious effects on the patient, such as infection, bleeding, and impotence. Despite my concern about the overuse of biopsy, I don't ascribe to the concern that that biopsies spread cancer.

Abstract 5022, Mortality from Biopsy

Only one previous study has evaluated mortality following prostate biopsy (Gallinal, Int J Cancer 2008;123:647-52). They reported an increase of 2 deaths per 1,000 biopsies.

◆**Methods:** Extracted data from the PLCO study.

◆**Results:** Among 12,300 prostate biopsies, 36 deaths occurred within 120 days: Thirty-two deaths out of 9,124 (0.35%) occurred in the positive biopsy group compared to 4 out of 3,176 (0.13%) in the negative biopsy group. In this latest group, this represents 1.3 deaths per 1,000 biopsies.

◆**Conclusions:** The mortality rate at 120 days following prostate biopsy of 1.3 deaths per 1,000 biopsies, in a population free of cancer, is a serious concern for the computation of benefit risk associated with PSA testing. This figure is in line with the risk reported by Gallina et al (2008) and is now based on a properly monitored population. This prostatic biopsy mortality would occur earlier than any benefit from a screening program and could reverse any potential gain from screening such as recorded in ERSPC study.

◆**Comment:** PSA screening followed by random biopsy was shown to reduce all-cause mortality in a 180,000 man study done in Europe. However, the US Preventative Services Task Force has cautioned that the negative effect of unnecessary treatment in men with low-grade prostate cancer outweighs the survival benefits. Studies like this one show there is a small but real risk of death from prostate biopsy. This is a strong indication that some form of imaging such as multiparametric MRI or Color Doppler ultrasound should be performed rather than jumping immediately to a random needle biopsy.

Final Thoughts

Although no groundbreaking treatments were presented at this year's urology and oncology meetings, some thought provoking study results were presented. Xtandi shows important advancements that could potentially revolutionize hormone treatment, providing an attractive alternative for men with intermediate stage prostate cancer. Reports are providing strong evidence that supplements and pharmaceuticals like Aspirin, Metformin, Sulforaphane, Polyphenols and Vitamin D have genuine, visible anti-cancer effects. Lastly, a rigorous study further confirms that subjecting men to prostate biopsies can be unnecessarily dangerous, even fatal. Hopefully, prostate imaging rather than biopsy will become the first course of action for evaluating men with high PSA levels. □