



## Foundation for Urological Research

---

# Foundation for Urological Research Newsletter

Spring 2010.....Volume 10 Number 1

### **Prostate cancer in the news**

The past several months have seen several prostate cancer related headlines both in the print and televised media. Interestingly enough, the issues addressed have been on either end of the prostate cancer spectrum. I will review the news on the early side of the spectrum, namely screening and early detection, and the recent publication of American Cancer Society guidelines and American Urologic Association guidelines with regard to screening. I will also review the other side of the disease spectrum, namely advanced prostate cancer, where the news has resolved around a newly FDA approved therapy, Provenge. There has also been very interesting and unique data published from our center dealing with the effect that treatments have on quality-of-life that will be dealt with as well in this issue of the newsletter.

The concept of screening or early detection of prostate cancer, or for that matter any malignancy, certainly makes logical sense. Finding disease earlier permits more successful application of therapy so as to ensure the highest possibility of cure of disease. Prostate cancer death has been on the decrease since the early 1990s after the institution of PSA screening and it is not unreasonable to believe that at least a portion of this decrease is due to screening and early detection. Other contributing factors include better application of therapy

technology, for instance improved surgical technique and also improved are a number of other modifying factors that could contribute to this decrease in mortality. As one example, there is evidence that the use of statins, drugs to reduce cholesterol, can decrease the incidence and the aggressiveness of prostate cancer. Over the past two decades, an increasing number of men have been placed on statins for lipid control. These other possible explanations aside, what could be the objection to a screening policy? To address this question, it is important to realize that a number of men who undergo screening and are found to have a diagnosis of prostate cancer will not benefit – namely those men who would never otherwise have been diagnosed with cancer during their lifetime and therefore would never have had to deal with the diagnosis, treatment decisions, and side effects secondary to treatment. The reason for this over diagnosis is that prostate cancer is found with increasing frequency in the aging male. This is often described as there being a large reservoir of prostate cancer for detection. Therefore, if sought after diligently enough, this reservoir will be tapped, and a group of men for whom therapy is not necessary to extend or improve their quality of life will likely receive treatment. You might say that the answer is to select for therapy those patients at greatest risk for aggressive cancer. Unfortunately with current testing, it is very difficult to identify with a degree of certainty, for each individual, if they carry

the lethal variety of cancer. Therefore it is not possible to assure a patient that treatment is unnecessary and indeed inadvisable. To be able to make that distinction represents one of the primary research interests of our prostate program as many as well as many others in the world. However, until this becomes possible, the diagnosis of cancer inevitably sets the wheels in motion to therapy. Statistics show that the majority of men, and understandably so, do not wish to stand idle after a cancer diagnosis is made. While they may understand that their cancer may not be problematic, they would rather be proactive and choose treatment.

In the spring of this year 2 large clinical trials testing the benefit of screening on prostate cancer mortality were published. They were the subject of discussion and controversy because while one study from the US, sponsored by the National Cancer Institute, revealed no benefit in decreased mortality, at least for the approximately 10 years it had been ongoing. A larger trial conducted in Europe did show a reduction in mortality among men who were screened. However, when one looks at the two trials there are obvious differences, some of which are culturally driven. Just as one example, but a very important example is as follows-- in the US trial, almost 50% of men who were randomized to the non-screening arm had, of their own volition, requested and obtained a PSA test done and therefore the trial was really a measure of programmed screening versus individual subject initiated screening. In Europe men are much less likely to seek PSA testing. Therefore, in the European trial, only 6% of patients randomized to no screening obtained a PSA test so this study was more accurate in the comparison of screen versus non-screen populations

The American Cancer Society issued their new guidelines in 2010. These guidelines emphasize the importance of informing and educating a patient about the possible harms as well as the benefits of screening. In 2002 the guideline suggested offering screening to men with the advisory that information concerning the pros and cons be discussed. The 2010 guidelines state that again, namely that the informed patient is important, and that the patient makes the decision of screening versus non-screening. So the guideline has changed its terminology in that rather than offering the PSA test with caveats, now information is the primary event and this is followed by the decision of the patient or the primary care provider. Clearly the decision as to whether to screen or not be screened is a personal one. And the reasons supporting the decision can be quite arbitrary.

Statistics do show that many men have PSA testing on a routine basis and have not discussed the issue with their physician nor are they aware that a PSA test was performed. So the information and discussion issue is vital to any informed decision this is specifically true in view of the fact that when the public is asked as to the relative risk/benefit ratio screening, they are much more optimistic about the benefits of screening than are substantiated by actual statistics for example a recent study showed that 1400 men would need to undergo screening to save one life.

The American Urologic Association has issued a guideline that men should, after appropriate counseling and information has been delivered, be offered a baseline PSA at age 40. This level helps to determine future risk of cancer and also permits a reference for future PSAs based on the baseline PSA level. Many men, whose life expectancy is estimated to be less than 10 years based on

age or other diseases, should not undergo PSA testing since the likelihood of prostate cancer compromising their duration or quality-of-life is extraordinarily small

### **Provenge approved by FDA**

Provenge belongs to an entirely new class of therapy, termed immunotherapy, which promises to provide additional options not only for patients with prostate cancer but for other malignancies as well. In the future, immunotherapy may become the fourth modality in the treatment of cancers joining with surgery, radiation therapy, and chemotherapy that have been the traditional mainstays in treatment to this date.

The Provenge story began in the late 1980s and early 1990s when scientists were able to demonstrate a strong immune reaction in the prostate of laboratory animals whose immune system had been sensitized to a specific protein produced by the prostate called prostate acid phosphatase. Rationalizing that this immune reaction could be duplicated anywhere in the body where prostate cancer cells producing prostate acid phosphatase had metastasized. Early investigative protocols were established to harvest patient's immune cells, specifically dendritic core antigen presenting cells were taken, exposed to prostate acid phosphatase which was made even more reactive by fusing it with another protein that stimulated immune reaction. These activated cells were returned to the patient by intravenous infusion. These activated dendritic cells would then traffic throughout the body, seek and destroy, or at least contain deposits of prostate cancer cells in "smart bomb" fashion. This strategy appeared to delay tumor growth and, furthermore, could be accomplished with minimal side effects. However, the actual success of such an intervention could only

be tested in a clinical trial to determine if patients receiving their newly stimulated/educated immune cells would survive longer than those patients who did not receive this immune intervention. The first small trial of 127 patients analyzed in 2007 did demonstrate a statistically significant survival benefit for those patients receiving Provenge. The FDA mandated that a larger trial be performed to confirm these results. This trial which enrolled 512 patients confirmed a survival benefit. The FDA, after further scrutiny, announced on April 29, 2010 that this therapy received their approval for delivery to patients with advanced metastatic prostate cancer who had been treated with traditional androgen deprivation, but whose disease now was demonstrating signs of progression. The therapy is completed in a 4 to 6 week time period and, again, is associated with very few side effects. The ability to extend survival without diminishing quality of life with severe side effects, which is often the case with chemotherapy, makes immunotherapy (Provenge) a very attractive option. And, as is often the case with a first in class FDA approval, there will now be a greater level of enthusiasm and optimism to pursue other avenues of immune therapy. Hopefully, in the near future a diverse menu of possibilities for the treatment of prostate cancer and other malignancies will materialize.

### **Another prostate cancer question to ponder**

A strategy that needs to be considered, and in my opinion implemented, when screening for early detection is advised, involves reducing the incidence of prostate cancer diagnosis and is termed chemoprevention. If efforts are made to discover or uncover prostate cancer, then these efforts should be supplemented by chemoprevention. By

doing so, the diagnosis of some of the more indolent cases of disease, which we have already described as being problematic by way of unnecessary treatment and its related side effects, would be prevented.

Strategies to prevent cancer are certainly attractive and the concept dates back to our country's forefather, Benjamin Franklin, whose aphorism – “an ounce of prevention is worth a pound of cure” has withstood the test of time. The major challenge of a chemopreventive agent is as follows: it must be virtually side effect free as it will be applied in a well, healthy population, at risk for, but not suffering from the disease in question. Hippocrates' admonition of “first do no harm” clearly applies to any chemoprevention strategy.

Testosterone, an androgen or male hormone, is converted naturally by the body to an even more powerful hormone called dihydrotestosterone. This conversion is accomplished by an enzyme five alpha reductase. Drugs, called five alpha reductase inhibitors have been synthesized. The first such drug, Proscar, or finasteride, blocked one of the two known 5 alpha reductase pathways. Proscar was used in a large clinical trial, the Prostate Cancer Prevention Trial (PCPT), to determine if it could reduce the incidence of prostate cancer by lowering dihydrotestosterone levels. The Prostate Cancer Prevention Trial was halted early when it was determined by the monitoring committee that a significant relative reduction of 25% in prostate cancer incidence was achieved in the finasteride arm of the study. These findings were published in 2004 in the New England Journal of Medicine.

In March of 2010, the New England Journal of Medicine, published the reports of a second chemopreventive trial, Reduction by Dutasteride of Prostate Cancer Events

(REDUCE), which tested another five alpha reductase inhibitor to reduce the incidence of prostate cancer. Dutasteride is a more potent 5-alpha reductase inhibitor which blocks both pathways that convert testosterone to dihydrotestosterone. It is therefore termed a dual 5-ARI inhibitor with anticipated greater efficacy as a result. Approximately 8,000 men were randomized to either Dutasteride or placebo. All men were scheduled for a prostate biopsy at 2 and 4 years following randomization. At both year 2 and 4, the biopsy incidence of prostate cancer was reduced by 22%. This reduction closely paralleled the results that had been reported in the PCPT trial. In addition, in both PCPT and REDUCE, urinary symptomatology, the incidence of urinary retention and surgery for obstructive symptoms were reduced

Level I evidence is the term used to describe outcomes derived from large, well constructed randomized controlled trials (RCT). Level I evidence is reinforced when more than one large RCT reaches the same conclusion. Urologists, and patients (men) have two very powerful trials to support prostate cancer prevention. The AUA / ASCO guideline and responses to frequently asked questions are available on <http://www.foundationforurologicalresearch.com/links.html> under the **American Society of Clinical Oncology (ASCO) Strategies to Prevent Prostate Cancer** heading. This information will be of great help to the patient in making a decision to pursue prostate cancer prevention. I believe that programs to promote screening / early detection should be coupled to a strategy of chemoprevention. If the frequency of prostate cancer diagnosis can be reduced within the lifetime of the host, then more research and resources can be directed towards those cancers which are not

prevented and which are more likely to be a threat to duration and quality of life.

### **Specimen Collection at EVMS**

The Biorepository at EVMS houses hundreds of thousands of tissue and fluid specimens donated to our research program by over thirty thousand generous patients. These specimens are collected from the hospital and clinical offices by the repository staff which consists of the Biorepository Manager, Mary Ann Clements and the Database Manager, Brian Main.

Schedules have to be juggled to provide for the harvest of afterhours specimens. A phone call starts the tissue collection process. The O.R. calls to let us know the specimen is on the way to the pathology department dissection room. We, in turn, alert our pathologist Dr. Dean Troyer, to let him know the specimen is on the way.

Once at the dissection room, the specimen is logged in, weighed and measured. Then the pathologist sections the specimen to prepare it for fixation. During the sectioning process, small pieces of tissue are cut from the specimen, frozen, and prepared for transport to the Biorepository. The frozen specimen is transported back to the lab in liquid nitrogen. In the lab, the specimen is cataloged and placed into a -80C/-112F freezer for storage. They will be available to the research staff for investigational analysis and correlations with serum, urine and other bodily fluids.

The bodily fluids come to us via courier twice a day. These fluid specimens are spun in a centrifuge to separate their various components then placed into small vials for freezing and subsequent distribution to the research staff where they are used to develop biomarkers for early detection and discrimination of aggressive vs. indolent urologic cancers or correlation with frozen tissue.

**The Perfect Gift** - This Father's Day make an gift to support the Foundation for Urological Research's efforts. Honor or memorialize your father, a friend or relative. Prostate cancer remains the most common cancer in American men, other than skin cancer. And, about 1 man in 6 will be diagnosed with prostate cancer during his lifetime. For a minimum contribution of \$10, the Foundation will send out a personalized tribute card which acknowledges your donation on the recipient's behalf. *Please make your gift by June 15 to allow time for mailing.*

**Throughout the Year** - Tribute gifts can be at any time of the year and are an excellent way to honor or memorialize friends and relatives on special occasions.

To make a gift, please call our office at (757) 457-5166 or Mail to;

Laurie Jackson, Director of Research  
Foundation for Urological Research  
6333 Center Drive  
Norfolk, Virginia 23502

Please provide the name and address of the tribute card recipient.