Active "Holistic" Surveillance

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I. Center for Holistic Urology Columbia University

I'm a urologist at Columbia University, and I've been there for about 20 years. My interest has been in prostate health and prostate cancer. I've been through the prostate cancer therapy wars with radical prostatectomy. I don't do them anymore. We now have robotic surgery, and there's a great robotics person at our hospital as well as some other institutions in the city. I do a lot of cryotherapy and have been through the "Cold War" using a lot of different technology both for patients who have recurrent cancer after radiation and those patients that have early disease that we can now focus in on with a focal ablation. My other passion and an area that will continue to be on the rise is active surveillance and using diet and nutrition along with herbal therapies, which I'll talk about this morning. It is not necessarily a cure, but many patients don't need to be cured because sometimes the risk of the cure is greater than the benefit. I'm not saying that no one needs treatment. Certainly we see a lot of men who have aggressive, early-stage disease who need therapy. I do believe that a lot of men who are diagnosed with prostate cancer in 2011 who have early-stage, non-aggressive, Gleason score 6 prostate cancer can be watched, and while they are watching a lot of men want to know what they can do, whether it be to change their diet or add a supplement that may allow the disease to be controlled even if not cured. Many urologists are starting to gain this as an accepted mode of therapy.

The amount of time that was spent during my 13 years of formal training as a urologist dealing with nutrition may have been about 30 minutes. Hopefully that will change. After I finished my urology training, however, I had the opportunity to work with Dr. Robert Atkins at the Atkins Center for Complementary Medicine. The prostate cancer patients that I saw there were changing their diets, and they were using herbs and other supplements. I thought they were crazy, but they were controlling their PSAs. I began to think there was some science behind it.

I established the Center for Holistic Urology at Columbia University in 1998, and our goal is to run human clinical trials, to develop multi-center trials, and to help educate patients.

II. Acupuncture

Acupuncture is gaining a lot of interest in the treatment of prostate cancer, and we have a dedicated acupuncturist at our Center at Columbia University. She has been taking care

of a lot of the patients that have pelvic pain. Anecdotally she has had some success with urinary incontinence, but the areas in which she has had tremendous success including treating young men in their thirties and forties who have chronic pelvic prostatitis, pelvic pain that just frustrates a lot of urologists. Another area is men with advanced prostate cancer who are on hormone therapy and develop hot flashes. They can be quite debilitating in some men, and we developed a study looking at this. They would come in once a week for about 14 weeks for acupuncture treatment, and then we would follow them and see how they did. According to the EPIC, which is a quality of life questionnaire to see how the patients feel overall about their lifestyle, many of the patients are doing better with acupuncture. Some of the men were having an average of around eight hot flashes a day, and by the end of the period, they were down to around four. It doesn't take it away completely, though it did in some of the men, and all of them were continuing, by the way, with their hormone therapy. The study suggested that acupuncture might provide a marked decrease in hot flashes experienced by prostate cancer patients receiving hormonal therapy. Acupuncture warrants further testing in a blinded RCT.

III. Why investigate CAM?

Complementary and alternative medicine should be investigated, and in large measure that is because there are patients out there that want the information. They hear about surgery, radiation and chemotherapy. They know about the side effects, and they want to know about what they can do for themselves. In addition, a lot of the patients have had a recurrence, and they want to know what they can learn about their recurrence, their PSA relapse. Conventional medicine may be helpful in that we know not all conventional therapies are 100% curative. One would like to think that complementary and alternative medicine is non-toxic, but that is not necessarily guaranteed. A dietary supplement cannot have any known side effects, and if that is found it will be pulled by the FDA.

Even though we feel that tumors are organ-confined, we know that they probably are not. There may be microscopic cells out there. If there is something that we can do holistically to drive patients into remission, that is a very important consideration.

IV. What to Look for in Natural Therapies

We would like natural therapies to have a known mechanism of action, and we would like evidence that it relieves symptoms. Demonstrated safety is important, as is the quality of the product. Patients have to buy these products themselves, and so we would like for it to be affordable. Many of the patients are Medicare patients and don't have additional income. Finally, it is key that the natural therapies don't interact with the other medications that patients may be taking.

V. Target Populations for Prevention

There are target populations for prevention, and the men that we should be focusing on are African American men, men with a family history of prostate cancer and men with an elevated PSA who go for a biopsy that doesn't show cancer but shows prostate intraepithelial neoplasia, PIN. Drug trials have looked at prevention with Proscar and Avodart, and they did reduce prostate cancer, but the caveat is that if you are taking these

drugs and you develop prostate cancer, you may develop a more aggressive form of the disease. We also probably need to look at patients with an elevated PSA who are biopsy-negative to see what we can do holistically for them. We also see men who are post-radical prostatectomy patients. Their PSAs aren't rising yet, but they have Gleason 8 cancer and a positive margin. They don't want to have radiation because it can increase the risk for urinary incontinence. They don't want to go on hormone therapy because there is no metastatic disease, and maybe their PSAs are still undetectable. Or maybe their PSA is just starting to creep up or they have had radiation and their PSA is rising. What can be done for these men?

VI. Approaches to Therapy

Medical therapy approaches include finasteride/dutasteride, which did show a reduction at around 25%, but it wasn't a home run because of the negative pathological finding that men who are on the medications may develop more aggressive cancer. There are studies that show that some of the NSAIDs may prevent prostate cancer. I check vitamin D levels in all of my patients, and I published a study in *Journal of Urology* last month showing that 75% of our over 3,000 prostate cancer patients are deficient in vitamin D. Dietary modifications are key, as is phytotherapy.

Inflammation is a risk factor for most cancers, and this is particularly in cases of chronic inflammation over time. Inflammation has also been linked to a number of conditions beyond just cancer including cardiovascular disease, Alzheimer's disease, diabetes, and several neurological disorders. There appears to be a nuclear on/off switch in the cells, and it's NF-κβ.

VII. Zyflamed

I went back and asked if any of the plants that are out there have been involved in anti-cancer drugs. There are a bunch of them, and some of the drugs, vincristine and vinblastine, are from plants and flowers. They are still used today to treat breast cancer, lymphomas and leukemias.

We set out to see if we could use an herbal approach to prevent prostate cancer, and I came across Zyflamend. It has eight different herbs, and each has low levels of anti-inflammatory processes. It was on the shelf, and a lot of my patients came in saying they were taking it for their joint pain and their PSAs were dropping. We did a number of studies in the lab, which took about three years to complete, which showed that it has a direct cytotoxic effect on cancer cells in culture. The cancer cells clump up and form apoptotic bodies or nuclear cell death.

Other investigators have gotten into it, as well, including MD Anderson looking at Zyflamed to see if it can shut off the particular gene product with cancer, which in fact it did. At higher doses it shut down NF-κβ, and if you shut that down, you can shut down the growth of cancer.

We opened up a clinical trial in men who had PIN cells to see if we could prevent and block the development of prostate cancer. It was basically a phase 1 trial lasting 18 months. The patients took the Zyflamed for 18 months and then had biopsies at baseline, 6 months, 12 months and 18 months. We also did history and physical examinations.

We did all kinds of blood tests to make sure that it really was safe and didn't interfere with anything else. We also wanted to make sure that it didn't interfere with testosterone levels, and because it's a non-steroidal, the IRB at Columbia made sure that we got EKG levels. We also stained the biopsies for the NF-κβ. We are now starting the phase 2 trial. We didn't see any toxicity except if you take it without food. If not, the patients got a bad taste in their mouths. If this was working as an inflammatory, C-reactive protein should go down, and in fact it did, 32% from baseline, which was statistically significant. This may also be a very good predictor of cardiac disease. There was no change in the testosterone levels, which was good, but we did see a change in PSA. Now remember PSA can go up in relation to infections in addition to prostate cancer. Over 22% of our patients had a 50% reduction in PSA, and I continue to see this. This is an important product. We found some patients that did develop cancer, but they were pretty small cancers, what I would consider to be clinically insignificant cancer. Sixty-two percent of the patients not only didn't have cancer, but they also didn't have any PIN, just benign tissue.

VIII. Lycopene

There has been other work on tomato extracts, lycopene, and there is some data showing that it can be healthy but some show that doesn't show much. If you are interested in taking it, watermelons have a lot of lycopene also. It is probably the highest antioxidant that we know about. There are about 72 studies in the literature on lycopene, and about half of them showed a decrease in prostate cancer. I think it is an important compound. There are lycopene pills, and a study that was conducted a few years ago showed that when men took lycopene before radical prostatectomy they actually had smaller tumors at the time of surgery than the men that didn't, and they had less surgical margins.

A lot of times you see these studies go back and forth, and it is hard to know. You have to look deep into the study to know whether or not it was powered correctly and controlled correctly. In another trial there didn't really seem to be a difference in the blood levels of lycopene in the men that did or did not develop prostate cancer. That was part of the prostate, lung and colorectal screening study.

IX. Soy

There is still a lot of controversy about soy. I personally believe that low levels of soy can be healthy, especially if you are exchanging it for fats and meats in your diet. Red meat should be eliminated or reduced, and if you do that, you want to take in some protein. Soy products are reasonable, and a number of studies have shown that soymilk and soy compounds have been shown to be healthy and can reduce prostate cancer growth. There are four types of isoflavones, and soy has isoflavones. Genistein has been shown to reduce DNA synthesis in LNCAP cells and inhibit the effect of testosterone in development of CaP in rats. Genestein may also be additive in patients undergoing radiation, which was published a few years ago by Ralph deVere White. With regard to soy and estrogen, a man would have to take a tremendous amount of soy to impact the testosterone level. It is a theoretical disadvantage, which I have not seen, and I also have not seen it make prostate cancer worse.

X. Pomegranates and Prostate Cancer

The other area that has gained a lot of interest is pomegranate extract juice or pills. The juice tends to have a lot of sugar in it, and I tell my patients they would do best with the pomegranate extract pills. In a study from UCLA, it was shown that the extract reduced PSA in the animal studies and prolonged survival. There has been a randomized trial in men that took pomegranate juice for a number of years and compared it to placebo. These were men that had radical prostatectomy already, and they looked at their PSA doubling time after surgery. At one year, their PSA doubling time was extended 11 months, at two years they doubled at 23 months, and at three years, they doubled at 39 months. It was published in *Clinical Cancer Research.*

XI. Fats

Men with higher BMI tend to have more cancers, more heart disease and more diabetes. With prostate cancer, a higher BMI can lower the patient's testosterone and raise the estrogen. A lot of the patients with a higher BMI actually have more aggressive disease at the time of diagnosis and can have a lower PSA at the time of diagnosis. It has been shown by groups at UCSF and Hopkins that just having a higher body mass index can put one's self at higher risk of recurrence after radical prostatectomy.

Participant

There was a study done several years ago, however, that in African American men a higher BMI put them at a decreased risk.

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For men that are considering active surveillance, there are still a lot of issues about going on to surveillance. We need to be aware of the risks and benefits of whatever plan is adopted.

XII. CAM and Prostate Cancer

Low-risk prostate cancer patients in active holistic surveillance generally feel better. They lose weight. They have more energy. The majority of the PSAs stay stable or go down. They don't develop erectile dysfunction, and they don't develop urinary incontinence. A potential down side is anxiety, which can't really be measured.

If they are going to consider surveillance, I tell my patients that it is reasonable to start a low-fat diet, eat more vegetables, and reduce red meat. I also think that they can drink wine. I don't think men should be supplementing with vitamin E and selenium unless they have had a bad week and aren't eating a lot of vegetables. Taking high doses of vitamin E can be dangerous; it can make patients bleed. Vitamin D is important, and I look forward to the University of Chicago study. Lycopene is important with some soy supplementation, along with pomegranate juice or extracts. Men should exchange their coffee and diet sodas for green tea, which is a very potent antioxidant. I do like the Zyflamend. There are two basic things in life for men also, which are diet and exercise.

XIII. Roles

It is right for patients to go on this active holistic surveillance if they are motivated and if they have low to intermediate risk, although I do have Gleason 7 patients on active surveillance that I watch. I recommend a PSA in the same lab every three months, and another imaging test is important. If I see that the tumor is going into the prostate capsule, the patients needs to go off surveillance and have treatment.

What about another biopsy? The repeat biopsy is important. My trigger point for re-biopsy is often the PSA doubling time. If it is more than two years, I am okay with that. If he has doubled within a year, then I am concerned. I would first get an MRI and then re-biopsy him. It is important to do it at another institution where the patient's initial biopsy wasn't done to have another pathology review to make sure that nothing worse is seen in the gland. I don't think age matters. I also find the PCA3 test, which is a urine marker, to be helpful especially in a guy who comes in with an elevated PSA and is concerned that he has cancer.

A number of mainstream medical centers are opening alternative medicine departments within their centers. Hopefully, they are conducting the studies that are needed. I think we will see more and more trials being conducted, and as long as good studies are being done, we can gain evidence and change practice patterns. We must also stress to patients that lifestyle is important, which includes eating properly, maintaining weight, and incorporating exercise.