

CANADIAN PROSTATE CANCER SUPPORT GROUP

Newmarket, Ontario

Volume 12, Issue 7, March 15th, 2008

**A support group that provides understanding,
hope and information to prostate cancer patients and their families**



Dr Juanita Crook our March Speaker, is the Head of the Princess Margaret Hospital/University Health Network prostate brachytherapy program. Over 900 men have been treated in this program since it was established in March 1999. Dr Crook's research in brachytherapy includes several articles on predictive factors for post implant toxicity and she is involved with the American Brachytherapy Society in establishing guidelines for the reporting of critical organ doses following brachytherapy. She has led the way in the use of MRI-CT for quality assurance of prostate brachytherapy and is involved with the ABS Working Group on issues of prostate contouring following brachytherapy. In addition, Dr Crook was one of the Canadian pioneers on the use of intermittent androgen suppression for recurrent or metastatic prostate cancer, establishing a Phase 2 trial in Ottawa in 1993. She is currently the NCIC Principle Investigator on an Intergroup study of the use of Intermittent Androgen Suppression for the management of a rising PSA following prostate radiotherapy. Come out to the meeting, and hear Dr. Crook

Meeting Date: March 20th, 2008

**Place: Newmarket Seniors Meeting Place
474 Davis Drive, Newmarket**

Time: 7:00 to 9:00 pm

Speaker: Dr. Juanita Crook, Princess Margaret Hospital

Subject: "Brachytherapy & Intermittent Androgen Suppression"

Canadian Prostate Cancer Support Group,
Newmarket, Ontario. 905-830-0447

a member of the



Canadian Prostate Cancer Network

Assisted by the Canadian Cancer Society
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The Newmarket Prostate Cancer Support Group does not recommend products, treatment modalities, medications, or physicians. All information is, however, freely shared.

February speaker notes **Dr. Richard Casey,** **Medical Director, The Male Health Centres**

Subject: “Hormone Therapy & Prostate Cancer”

Dr. Casey our speaker at the February meeting, focussed most of his talk on those of us who have prostate cancer metastasizing into our bones. He introduced us to some of the new drugs that are under clinical trials at the present time. He made a strong pitch for those who are at that point in our lives where Chemo is the next step, that we should talk to our doctor about getting in on a trial. Here is what he had to say.

I have restricted my practice to two things, sexual problems and prostate cancer and what we say is, if you come and see me and you don't have sexual problems before you come, after I've finished with you, you will have sexual problems. Tonight I am going to talk about an area of prostate cancer where there's a lot of research and put on my other hat but I won't talk too long as these sessions are always good when there is time for some interaction and some questions. I do not know the right way to treat prostate cancer. I wish I did. When patients come to me and say, Dr. Casey, are you the right person to treat my prostate cancer? I say, no, but I will send you to someone who thinks they are. As you know, if you have ten urologists here, you'll get ten different opinions. That's the difficulty in having prostate cancer. I learn a lot from my patients. My practice is about 85-90% men. I learn a lot about their lives. I learn a lot about death. I had a fellow in my practice the other day who I've known for about 30 years. He's been married for about 50 years and his wife has just passed on about a month before he came into my practice. When he told me that I said you must be very sad. He said it's horrible, I don't know what I'm going to do. I said, Why did you come today? He said, Does that Viagra stuff really work? He had gotten some casseroles at the funeral and he's moving on to another relationship. So, tonight I'm going to talk about prostate cancer, and you know there are 3,500 deaths a year in Canada from prostate cancer. This number is increasing because more people are getting prostate cancer and we get about 10,000 new cases a year. That's a pretty big number. This has changed quite a bit since I started. The growth projection in the next few years will be upwards. 3000 deaths a couple of years ago, 6000 deaths a few years from now. It means we're doing a good job in diagnosing cancer because there are many more cases that we're finding that are dying but most of the advances now are towards those men that eventually die from prostate cancer who have had hormone therapy.

A lot of research is going on and I can maybe help you get involved in clinical trials which many physicians are conducting and I'm sure many of you are interested in. So, we're talking about hormone refractory disease, which is what happens with prostate cancer before you get really sick and possibly die from it. I want to talk a bit about what I do. Other than having a urological practice, I run a research company called CMX Research. We are a consortium of about 50 urologists from across the country. We do clinical trials for drug

companies primarily, most of it is prostate cancer related. When Zoladex and Lupron were introduced, we did the clinical trial work to see if they worked. When Viagra first came along, we were the guys in Canada that tested it. We also tested Docetaxil, Casodex and a lot of the drugs that you are familiar with. We did some of the earlier work. We didn't make up the trials, we just executed them, the drug companies decide what to do and we do them. We've noticed that recently there are a lot more clinical trials for prostate cancer and they are directed at men who have had the cancer treated and the cancer is still there or coming back. That's about 50% of men who have had treatments, they may have had a prostatectomy, or radiation or brachytherapy. There's a 50% chance that your PSA will rise again, usually just enough to drive you nuts. In about half of the 50% it continues to go up and that's where most of the research is directed. It is trying to prevent those cancer deaths or at least postpone them. Dr. Liguornik and his group in Newmarket are active as a part of our group, they are active in clinical trials and I like urologists who are active in trials because they know what's coming in down the pipe and they can also advise you on more treatment options you should be thinking about.

So, what's going on in prostate cancer right now? There's a lot going on in prevention. There are a number of drugs that are used for breast cancer that are now being tested in men who are at high risk for prostate cancer. Who's at high risk for prostate cancer? Well, if you have a brother who has prostate cancer, there's a very good chance you'll get prostate cancer. If your father had it... I'm sure you all got the same advice from your urologist, if you have a brother, go tell him that you have prostate cancer and he should go see his doctor. If you didn't get that advice, you should have. There are a number of trials at an American company called GTX, using drugs like Avodart and Proscar to prevent prostate cancer in watchful waiting. What's happening in the last five or ten years, is that since PSA means nothing any more, I am sure you've had your PSA talk. Dr. Fleshner says that anyone with a PSA over 50 or over 2 should have a biopsy and maybe he's correct. We're coming to the point where every man over 50 is going to get a biopsy of his prostate, like we're suggesting a colonoscopy. I don't know if we're there yet. Certainly there's a growing group of guys who get prostate cancer who don't get treatment. They stay on watchful waiting because they and their doctor decide not to have surgery or radiation and want to wait and see what happens. Most guys want to take

charge. I have men in their eighties who have prostate cancer who say, "Doc. why can't you cut out my prostate gland". I tell them that we could but they wouldn't be half the man they are now, after that type of surgery at eighty. So, watchful waiting is a huge growing area. It has such an impact on surgical wait times because before this concept was pioneered by Dr. Laurence Klotz and accepted by the urological community and it's just the last few years that it has been, surgical waiting times were significant. This represented about half of the surgeries we were doing, guys who may not need surgery. Now that we're watching these fellows and finding that most of the guys that we watched had very benign forms of prostate cancer, we want to get a little bit greedier and say, can we not only watch them but can we give them something to get rid of the cancer so they don't have to worry about their PSA every three months. Drugs like Avodart and Proscar are being used. It's a trial that Dr. Fleshner has designed, called the Redeem Trial, which is where men who are watchful waiting were then put on Avodart to see what happens to their PSA and their prostate cancer. The trial is still early but there's an indication that it may have a major impact on slowing the prostate cancer. So, those of you who are on watchful waiting, instead of the inevitable surgery or radiation five or six years later, may never have to face the bullet. If this trial brings back positive results, just about every guy at risk for prostate cancer is going to be on Avodart. If it works, it's going to reduce prostate cancer by 30 to 40%. Better news is that it's good for hair growth, the bad news is that it's an expensive drug. There are two sides to every treatment and probably will cost about \$100 a month. It is not likely that drug plans are going to pay that. Would you pay \$1,000 a year not to have prostate cancer? Most of us would.

I was at a very important meeting in Cancun recently, called International Controversies in Prostate Care chaired by Dr. John Trackenburg. I was speaking to a fellow from UCLA who was doing a trial on pomegranates. He is running a huge multi-million dollar trial in the United States, looking at pomegranate extract and men with prostate cancer. He says the preliminary data looks very good and men who have prostate cancer, who take pomegranate juice, their PSA rise slows down. It's all a matter of slowing it down so that you can die from something else. The pomegranate study is very encouraging and we're trying to bring it to Canada. It's harder to do the trial in Canada with a health product than it is to do it in the United States. There are very little regulatory issues in the States, whereas in Canada, to make claims for a health food, you have to be very stringent in what you do. We're trying to get it through Health Canada so we can use this trial. What I do take from this, if you take something natural, consider pomegranate juice. There may be some science to it but why wait. The preliminary science is very encouraging and I am suggesting that my patients who have had treatment and have residual PSAs drink pomegranate juice on a regular basis. As you know, every month there is a new health food to take but this certainly has had enough interest in it that the

pomegranate company in the United States has put over \$20 million into the trials, so they feel very strongly about this. Another drug that is in research, those of you who take Zoladex, Lupron or Eligard, there's a whole new class of drugs coming along that may not have the same side effects profile. These drugs have horrible side effects. There's a whole bunch of new LHRH drugs, so there are opportunities there. When you talk to your doctor about it, ask him if he's involved in any of the trials on these new drugs. Maybe he'll be able to switch you from the drug you're on to a drug which will have less side effects.

I really want to talk about Hormone Refractory Disease, which is a disease that kills men with prostate cancer. Very few of us die from prostate cancer that isn't Hormone Refractory Disease. Very few men who will succumb to the disease haven't been on hormonal therapy. It's almost a natural history of the disease. Who of you has had Zometa? This is a bone hardening agent and you've realized, probably a bit late, that the hormone therapy we've been giving men is slowly destroying their bones. We're giving men treatment for prostate cancer, controlling their PSA, but, destroying their bones enabling them to develop horrible bone disease, painful bone lesions and eventually leading to fractured hips and fractured spine. A Montreal urologist was the first to work with Zometa, which is an intravenous disphosphate, like some bone hardening agents you are now taking, or your partners are taking because the incidence of osteoporosis is so much greater in women. When Zometa first came out they were restricted to men who had metastatic prostate cancer and were in dire straits. You have bone pain so you go to your radiation oncologist to have radiation and they would say that maybe you should try Zometa, which is an infusion, an injection, about \$400. What's happened is that we've realized that it works so well that we're starting to roll it back and using it for men before they have metastatic disease and I'm sure that those of you now who have gone to the doctor and are on LHRH are also on vitamin D and calcium. If you're not, you should be but I'm sure you are. What's going to happen now, you're going to get Vitamin D, calcium, bone density tests and, if your bone density is low, a shot of Zometa, to toughen up your bones early on so you don't have to deal with the bone density later on. There's increasing evidence that if you take these agents early, since the battle for life with prostate cancer is fought in the bones, you can slow down the progression and it's a survival benefit. It's slow and it's unfortunate that the government only funds evidence based therapies but those of you who are interested in the disease, shop around a bit before it's actually considered evidence based. I recommend to most of my clients who are on LHRH to get a bone density, to go on an antiosteoporosis product. In five years it's going to be a standard of care. There's another drug administered as a vaccination, which is quite different as you take it once a year and it hardens your bones and prevents osteoporosis. We're in clinical trials for it for men with metastatic disease, (Dr. Liquornik is involved, in Newmarket) this is again to slow

down the progression of prostate cancer once it is in your bones. It's a simple vaccination and I think they are going to hit a home run with this drug, it looks very good. It's not only for prostate cancer patients but also for men and women with osteoporosis.

The one drug I want to talk about tonight is an inhibitor. Anyone here hear about a drug called (Xinlay?). It was a drug that had been tested in Canada a few years ago, while it had some action in the United States, it was really a bit of a flop. It didn't have the action we thought it would. I had a number of patients on the trial who were on the drug and their PSA stopped rising. They had been having a dramatic rise in their PSA and the drug stopped it from rising. It didn't go down, it just stopped going up. They remained in my practice and their PSA remains either stable or rising very very slowly. So there is some action. Based on that another company, Astra Zenaca, decided maybe we'll follow that along and get a better drug that works. Endothelin inhibitors are a class of drugs that prevent the tumour from growing but they don't kill the cancer. The good part about drugs that prevent growth, they are called statins, they keep the growth static but they don't have the side effects. Toxic drugs that kill the cancer and make your PSA go to zero, kill a lot of innocent bystanders at the same time, like your gut and skin problems, so these drugs that have a static effect are very good because they are very well tolerated and they are usually in pill form. If your PSA is 30 or 40 and it's doubling every three or four months, if they can stop that from doubling or slow it down, you can improve your life expectancy. If you look at the prostate cancer continuum, most people that have successful local therapy, God bless you, you've been lucky. About 50% of men don't, so they've had the local therapy and they go on to heavy duty: radiation or hormone therapy. The average time you are on hormone therapy varies and it used to be about five years but, since we use it so much earlier now, it can be as long as eight or ten years. Eventually, if you live long enough, this hormonal therapy will fail in about 70% of men. Some men, you give them a few shots of Zoladex and you never hear from them again and it never comes back. But most men continue to progress and, as you can see, when the PSA rises then you have about a 24 month period, depending on your rising PSA before you're in big trouble. So you've had hormone therapy, your PSA's been zero, now you're starting to go back and it's 2, it's 4, 6. You have a window, we know that in the next couple of years you are going to be in big trouble. That big trouble is, you're going to die. It really depends on how fast your PSA goes up. It's this area where there's absolutely no treatment available. If you're on androgen deprivation therapy and you've been on five or six years and your PSA starts to rise, your doctor is just watching your PSA most of the time and scratching his head and saying that it's not so bad. What we eventually do is take a bone scan and when it finally gets into your bones we refer you to a clinical oncologist. Right now the standard of care is for your oncologist to say that, yes, it's in your bones but you're not sick

enough to have chemotherapy and most of us, when we hear the work chemotherapy, we say, "No thank you, I don't want that." Because, right now, the advantages of chemotherapy are three, six, maybe seven months of improved survival. When you think of the side effects and the improved survival, it isn't that great. For some men though, we think, if we use the chemotherapy earlier, when there is maybe more than three months potential survival it maybe a good idea. However, when you go to an oncologist and ask what's the average time I'm going to get by taking chemo, he'll likely say three months. That's what the clinical studies show. But that's probably not true of most of us. If you go early and get treated aggressively and you're young and relatively healthy, you can get a fairly good improvement. A lot of research is being done on that two year period of time, when your PSA starts to rise to when you're due to have chemotherapy, We all go through that period unless we get hit by a car or die of a heart attack. It's a tough period for most men to go through. They see their PSA rising and don't know what to do about it. Once you become symptomatic, once you have Hormone Refractory Disease, in other words the hormone treatments aren't working and you start to have symptoms, you have less than a year of life expectancy. Now, there are exceptions to every rule. I'm sure there are many here and that's great but statistics catch up to all of us and this is really where we want to direct our attention.

The area we really want to talk about here is the period of time after you become bio-chemically relapsed. There's not much time between then and chemotherapy. What can your doctor do if you go to him with a rising PSA, they can put you on some Casodex, which will give you a transient drop in your PSA. There are some other agents like prednisone, which can give you a temporary relief but really, in most cases, you're treating the PSA and the anxieties surrounding the PSA and not having a major impact on life expectancy. There is chemotherapy and you've probably heard a lot about that, or there are investigational agents. When you do your homework and go to your doctor and you know you're in trouble and your doctor says "I don't know what to do.", always ask him what's going on in clinical trials, is there something at Princess Margaret? Is there something in town that I can consider? Because most of the clinical trials in cancer have a perceived advantage for patients. Health Canada will not allow us to do placebo based trials in cancer if there's a better treatment available. So, you'll never be deprived of better treatment or the standard of care if you go onto one of these clinical trials, you'll always get something you wouldn't get or nothing at all, which is what you're getting right now. So, the worst thing in getting involved in a clinical trial, is you'll get the same as you're getting right now and the best is you'll get something that may be amazing. Granted, sex is not cancer but when Viagra came to us and said we have a drug that we think causes erections, we said there's no drug on the planet that will do that. There were no treatments available and all kinds got Viagra seven or eight years before it was released and it was an amazing improvement in the qual-

ity of their life. There are other areas of cancer where we see this. Clinical trials, while they may have a bit of a bad name because some of the trials where they deal with very, very sick men or women, there can be problems but with prostate cancer, we're lucky, because most men involved in clinical trials are relatively healthy, they are just watching their PSA.

So one of the things I want to talk about tonight is something that we may see in the next couple of years. It doesn't have a name yet, it's ZD4054 and it's an oral agent. As you know clinical trials are very expensive because they have to be done under strict, rigorous scientific protocol and they have to withstand the peer review, people are very critical of it. Most clinical trials for a new drug are costly. To get a new drug from lab to market costs about \$600 to \$800 million and these drug companies invest significant money early on in hundreds of millions of dollars and only one in seven ever gets to market. I've been involved with drugs that have almost gotten to market that have cost the company three or four hundred million dollars and it's a write off because they can't use the drug. This drug is farther along, it's in phase two trials. A phase one trial is where we have discovered a molecule, it's been used on rats, the rats haven't died, now we've got to give it to some people to see if they die and find out what the right dose is. These are volunteers early on. When it gets to phase two they are looking at it and seeing whether it works or not. And when we get to phase 2B, we know it works but we want to know who it works on. Then in phase three we have a good idea that it works, we have a good idea of the dosage and we want to see in at least a thousand people, what the results are. Sometimes it takes tens of thousands of patients before you know the drug is unsafe. Take for example, one called Bacal, which was a great blockbuster, tested on thousands of people and was finally released and sold ... 12 people died from the drug. It was such a popular drug, so many people took it but it caused liver damage and 12 people died so they had to pull the drug back. So drugs can be out on the market before they are discovered to be unsafe but this drug appears to be safe.

Our cells all through our body have receptors. They have testosterone receptors, muscle cells have muscle receptors and that's how our body works. A chemical messenger goes to the cell and tells the cell what to do. Think of it as a docking site. So all of our cells have docking sites for the chemicals that circulate in our blood and certain chemicals dock on certain cells and tell them what to do. The endothelin receptors are docking sites on cancer cells and there are docking sites on normal cells as well but there are more of them on cancer cells because cancer cells don't know what they are doing. They are improperly producing a lot of chemicals. So all these receptors with docking sites on cancer cells and some of the receptors cause the disease to grow quicker and to multiply and other receptors cause the cell to die. So you can invent a drug, like Casodex which is a blocker, it sits on a testosterone receptor in prostate cancer cells and prevents testosterone from getting in there. The cell thinks the testos-

one is already there because of the receptor blocker. This drug that we're talking about is a blocker for a special receptor that is responsible for the cell to grow. So, if the drug can block the receptor, it blocks actions of that receptor. So, the endothelin blockers, what they do is they stop the cell from receiving the chemical message and things happen. It slows down the metastases, it slows down the progression and it slows down new vessel formations. When cancer cells grow and they spread through the body, they have to send a signal out and produce blood vessels and it prevents that as well. If we can find something to block the other endothelin receptor, which causes septosis, which is cell death, we want to find something that stimulates that so we can kill the cell. Again, we're also talking about something to slow down cell growth, that can block an action that all our cells have.

There's a clinical study that we're doing now, that I think Dr. Liquornik and number of other urologists are doing. So if any of you are interested please email me and I'll direct you to the right contact. They are taking men who have had hormone therapy, whose PSA is now rising and they are waiting to get chemotherapy. They are comparing it to a placebo, which they can use in this trial as there's no treatment available, comparing it to two separate doses. A lot of these men are eligible, we're looking at progression and survival. To a scientist, progression is important. To a patient, survival is important. Many of us die with prostate cancer, with a PSA that is rising, from something else entirely. Really, the most important thing that comes from this is survival. When regulatory bodies look at it and doctors look at it they want to know if the disease has been altered. If the disease is still growing, we can't say that it helps survival. So, the trial is being done, the median age is men about 70 who have problems. If the PSA is rising and you're 82 years old, it's not likely that it's going to be a big issue but, if you're 70, you still have another 10,15 years left of life. These men had an average PSA of about 187, so these are guys that have high PSAs. The side effects of this drug are minimal, just a little bit of swelling in the ankles and a redness of the face, the pill is very well tolerated. Remember, this is an effect we see in men that are in big trouble, they have PSAs of 150, they have life expectancy of less than a year and we are able to improve their life expectancy with an oral agent that's very well tolerated. The clinicians look at this and say, "Look, if it works well in guys who are in big trouble, maybe we should use it a bit earlier. Maybe we should use it so early that eventually we use it instead of hormonal therapy." That's what is exciting about these pills. They are something that we can start out with the sick guy and eventually roll it back and use it earlier. Anybody who's been on hormonal therapy can tell you that if they can use something else other than hormones, they would have done it. So these new oral agents are very exciting but remember that they are static agents — they are not killing the cancer, they are slowing it down. If you take a bad group of patients, the average improvement was six months, a half year survival. It's not a lot but 50% more than

you would have had. When you read this and you say, "Well, I don't want to go on chemotherapy, they're only going to give me another six months." Well the quality of life of these patients is pretty poor. It will improve the quality of life and give another six months that they wouldn't have had, maybe live long enough to try another clinical trial. So, for this population, six months is very significant, better than chemotherapy, which is extremely expensive and fairly toxic. So what we can say right now is that this drug prolongs survival in patients who have Hormonal Refractory Disease and bone metastasis. It's very safe and, if these results confirm in larger trials which we are starting now, it's could be a significant breakthrough in the treatment of prostate cancer. I think the take home message is the research is being done in the tail

end of prostate cancer, because that's where we're doing a bad job.

There are 5,000 men a year in Canada who die from prostate cancer. Only about 1,000 of those men are getting chemotherapy. It may be that others are scared of chemo or have other health issues that prevent them from getting it. Right now only half the men who would benefit from chemotherapy are getting it. Add to that the fact that there are now some new oral agents available and they are available for free in Canada in the form of clinical trials. If you have prostate cancer and it's smouldering along, get in touch with your doctor to direct you to a place where you might have a chance to join a trial. Not only may it benefit you but you might benefit the whole of science as well.

New therapies for prostate cancer are tested in clinical trials.

Clinical trials are organized studies conducted in patients and are required before a particular treatment can be made available to the public. They are conducted to answer specific questions about new treatments: to test new ways of using established treatments and to test the safety and effectiveness of a treatment.

Every clinical trial is designed to answer a specific set of questions about a treatment. Each study enrolls patients with certain types and stages of cancer and certain health status. If you fit the criteria for a clinical trial, you may be eligible to take part.

You would most likely be referred to a trial by your own doctor or by a doctor who knows your case. You must have a reasonable understanding of the possible risks and benefits of a clinical trial and be freely willing to take part in it. All patients in clinical trials are carefully monitored during and after participating in the trial. Be sure to talk to your doctor about whether you would be eligible to participate in a clinical trial.

Types of Trials

Clinical trials are carried out in phases, each designed to find out a certain type of information about a particular treatment. Information from each phase is built upon in the next phase; all of the information collected on the treatment is used to obtain approval for its use.

Phase I Trial involves a small number of patients. It tests how to give a treatment and how much can be given and it identifies any side effects caused by the treatment

Phase II Trial involves 20-50 patients with a particular stage or type of cancer. It tests the effectiveness of the treatment in treating cancer and it determines the frequency of side effects caused by the treatment

Phase III Trial involves large numbers of patients (in the thousands) it compares the effectiveness and side effects of a standard treatment and the new treatment in treating cancer. The patients in these trials are assigned randomly to receive one of the treatments being studied.

Speakers for our 2008 meetings. Mark these dates on your calendar

- March 20th Dr. Juanita Crook, Princess Margaret Hospital
- April 17th Durhane Wong-Reiger, Pres. and CEO. Optimizing Health Org.
- May 15th Dr. Andrew Mather, PMH. on Depression
- June 19th Jerome Green, Urologist, Southlake Cancer Centre