April/2013 speaker . . . Dr. Padraig Warde, Radiation Oncologist
Subject: What's New in Prostate Cancer Treatment

Dr. Warde's talk at our April meeting focussed on the new drugs coming down the road to treat prostate cancer after hormones such as Casodex and Flutamide are no longer doing their job. He also, as usual answered a lot of questions on the whole spectrum of prostate cancer care. Here is what he had to say.

The whole point of taking hormones is to stop testosterone production.When you first go on hormones,they actually tell your testes to make more testosterone. They stimulates the testes to make more male hormones for about three to four weeks. During that time, generally people are prescribed hormones like Casodex or Flutamide. After about three or four weeks, the testicles stop making the male hormone and the cancer cells are starved. One of the new drugs on the market, called Firmagon - Degarelix. works directly here by preventing the male hormone, this LHRH from making the hormones. It works directly, there isn't any stimulation at the front. The nice thing is that it works much faster. If you're in a situation in which you need to drop the testosterone levels in 24-48 hours, this drug works very quickly. There's no need to give an anti-androgen with it. The only problem with it is that it is a monthly injection. You have to see the doctor once a month for the injection. All of the other drugs, like Zoladex which is every three months, Lupron generally every four months and some six months drugs out there, you don't see the doctor so often. They are currently trying to manufacture a formulation of Firmagon that allows it to be given every three months or every six months. This won't be on the market for the next few years. This is a drug that is now increasingly being used. I tend to use it only when I need to get a very quick response, for someone who has a very aggressive cancer. Most GPs tend to not to give this monthly, subcutaneous injection, so you must come to the cancer centre for it. This is the first really new agent that's come on the market in the last few years. It's not particularly exciting because it has a very limited role.

The next set of drugs are more interesting. I'm going to explain some medical terms here, Endocrine and Intracrine. What I mean by Endocrine is: the androgens are produced in the testicles and in the adrenal glands and go to the cancer cell and cause the cancer cell to grow. For years we were wondering why, after a number of years, these drugs stopped working and we became hormone resistant. We couldn't figure out why that was. We thought that maybe these drugs would stop the production of the male hormone. What we found out was that the actual cancer cells figured out a way to make their own male hormone in house. This production mechanism is called Intracrine. There are two new agents that have come on in the last year. One is called Aberaterone. The nice thing is that it's a pill and it blocks the male hormone being made both in the testicles and the adrenals and also within the cancer cells, in the actual tumour itself. That's the key difference here. Whereas these other drugs, before, stopped the making in the testicles and the adrenal glands but within the cancer itself it was still able to make the male hormone. In all of these things, the idea is good but the question is, Does it work?

A number of studies have been done, called the Cougar studies. When you start to test new drugs, you generally test them on people who have far advanced disease. These new drugs were initially tested on people who had had all the hormone treatments then had had chemotherapy, to see if there was any advantage that could be made, would it work in that group of people. They took 1200 patients, who had progressed to where the cancer had spread to the bone, they were castrate resistant to prostate cancer, they had to have failed one or two chemotherapy regimens. It was a very simple study. They gave two-thirds of them the new drug, Abiraterone plus Prednisone and the other participants got a placebo with prednisone. They wanted to see whether or not it improved the outcome. In other words, did it help people live longer and was it an effective treatment? There were 13 countries participating, and Canada contributed over 150 patients. The survival of patients who received the drug Abiraterone was much higher and much better than those who had the placebo. So much so that, early on in the study, (in studies, there are safety committees, people who have nothing to do with the study, who look at the results as they are coming in at certain defined points and, if the results of these new treatments look like it's really exciting and look like it's a real benefit to patients, the study is stopped and the patients who got the placebo are switched over) they stopped and offered the drug to all who hadn't received it. It didn't look like a huge benefit at this stage, of four months but you've got to remember that the people were very advanced, who had already had virtually every treatment under the sun, including drug treatment. That to us was a very star-

tling result. Not only did it benefit in terms of survival, people living longer, but it also did the response rate in every other area. In 40% of the people, their PSA dropped significantly. With that result in hand, they were very encouraged so they now moved it earlier in the disease, to people who hadn't had chemotherapy but still had failed in hormones: the PSA was still rising and the cancer had spread to the bones. They did the same type of study again, gave the same drug. The benefit again was startling in terms of people who are on the drug doing so much better in terms of progression free compared to people who were on the placebo. Again, this study was stopped early because the results were again startling and they were beginning to see that people were living significantly longer.

This is the first agent we're talking about, Abiraterone. It improves survival, it delays the progression of the disease and, for people who had very difficult symptoms when they were starting on it, compared to the sugar tablets, it kept them well for much longer. The other nice thing is, it's a tablet, there are no real safety concerns, it isn't something that is likely to make you incredibly sick. You have to be careful about blood pressure, because it could push up your blood pressure. It could also give you a very low potassium level, so your potassium has to be checked fairly regularly. Very rarely, it can affect the liver, so the liver has to be checked regularly. This was the first major break-through. You might say, "What's so great, four to six months" but, if we can now get this drug for people much earlier in the disease, say people who are getting radiation or have had surgery and seeing if it is as active there, it might actually allow us to cure more patients. To kill microscopic cancer cells at much earlier stages of the disease.

The other agent is Enzalutamide. When testosterone binds to an androgen receptor on the surface of the cancer cell, it goes in and does its thing with the inner nucleus at the centre of the cell. If we could stop the male hormone binding to this androgen receptor, this would be tremendously beneficial. The first set of drugs we had for that were Flutimide and Casodex but this drug is 1,000 to 10,000 times more effective at binding. What it does is it binds to the androgen receptor on the cancer cells, so the testosterone or the male hormone can't activate it. If it can't be activated, the cancer cells die. It is very, very potent as it blocks the effect of the male hormone coming in and binding to the androgen receptor. Again, the results are exactly the same as Abiraterone. Again it's a tablet that the only really major side effect that's been noted with it is some fatigue and tiredness. There is some concern that there might be some increase in seizures but again, it's very unlikely and is very rarely seen, if ever. This has just come on the market. Neither of these two drugs are covered yet by the government health plan for general use but that's only a matter of time, it will come in three to six months. The trouble is that Abiraterone, for example, costs about four and a half grand per month. Enzalutimide has just got Health Canada approval, it's just on the market and it should be available within the next three to six months.

There are some other new drugs that are all coming on the market. Some of them only have numbers. Tak-700 - Orteronel is not available yet but is in the marketing stage. It has been developed as a tablet. It's like Aberaterone but the trouble with Aberaterone is you have to take some prednisone along with it and prednisone, if you're on it for a long time can give its own set of problems. As an anecdote, the reason I'm small is not because I was born of small parents, they were reasonably tall and all my brothers are much taller than me. The reason is that I had prednisone when I was 10 years old because I was a very asthmatic. I'm still the same size that I was at 10 years of age. So Prednisone has it's own side effects, it's one of those things that, long term, we would prefer not to use it. So, if you can develope agents that don't require that you have to take prednisone with them, that's probably the way to go.

The next set of drugs, ARN-509, which has now gone into testing, is much more potent than Enzalutamide and the preliminary data on it is very exciting. All of these are new drugs. Let's role the story back a long time, 35, 40 years, when the first set of drugs started to be used in women for breast cancer, chemotherapy, called CMF, what we found at the time was that we were extending the life of the women who had advanced disease. In other words, we finally had drugs that worked. It was nice, it was good and it was very useful in that setting and it wasn't particularly loaded with side effects but the real beauty that came, it took those drugs and it brought them to women after their surgery. What those drugs did, if there was still a tiny amount of cancer, microscopic disease left behind or had travelled somewhere in the body, we have shown that, we can improve the cure rate quite significantly in some people.

This is where we are now with these new drugs. We're starting a study with Enzalutamide, hopefully within the year, with approximately 2500 patients across Canada and Australia, to see if by giving the drugs much earlier that we can improve the cure rate fairly dramatically. Drugs like Lupron and Zoladex certainly improved the cure rate a lot but we've been stuck at that level for 15 or 20 years. Zoladex has been on the market since the early 90s. This is the first set of really new agents that we can actually start to use that might move the cure rate a bit higher. That's the excitement with these new drugs. The fact, also that they do not particularly have any major side effects, though, with all of these new drugs, sometimes you do not get to see the side effects until you put them into general use in the population. We'll be keeping a fairly close eye on that.

I don't think I have anything more in the way of new drugs to talk about. In terms of newer chemotherapy agents, we've known about the drug called Doxitaxil for a long time. It works, it's effective, a Canadian study showed that we've improved the survival rate and it's been tested in an area of diseases. There are some newer chemotherapy agents that are out there but there's nothing particularly exciting. There is one drug that has been developed in Vancouver. They did it

based on laboratory work and worked it all the way up and it is now not taken over by a drug company but helped with a drug company to formulate it into a drug. People like myself don't advocate the business of making tablets and doing all that type of work developing formulas. It's somewhat promising but not as exciting as these new agents.

Here are a few of the questions he responded to.

Q. Do any of these drugs cause hot flashes?

A. Hot flashes and all those things are due to the withdrawal of the male hormone. It's not that the drugs themselves give the hot flashes. It's the fluctuating levels of the male hormone and the male hormone reduction. The side effects of fatigue, a little bit of weight gain and hot flashes, some changes in mood, yes, I'm afraid the use of hormone agents are in some ways much more efficient at dropping the male hormone levels, so you are still going to experience those side effects.

Q. When you say "cure", what does that mean?

A. When I use the word cure, what I mean is: in terms of when you've had radiation or a prostatectomy, in a proportion of people, they may not eradicate the cancer completely because a microscopic amount of the cancer may have already left the prostate. Where I'm looking in terms of a cure, if we can find a way to kill that microscopic amount of cancer that would be a cure.

Q. What effect would these have on your quality of life?

A. These new drugs are offering you another reason to be excited. Keeping in mind that the studies dealt with people with very advanced disease, at last we have drugs that extend time with minimal to no symptoms. In other words, it kept people feeling good during that time and their quality of life. compared to the people who took the placebo, it was immensely better.

Q. I work out a lot, does exercise increase my testosterone?

A. Not to my knowledge, in fact, we're actually recommending exercise. We have problems from a lot of these drugs with bone degeneration, with osteoporosis and also with muscle degeneration. Now we understand a lot more about them and, for people who start on hormones now, we recommend exercise, particularly weight bearing exercises are very important; taking vitamin D, probably more important than calcium; and checking the bone marrow density every year or two, because there are now other drugs on the market that can prevent that osteoporosis.

Exercise and cutting down on alcohol as well, not to zero, there's a whole list of things that we can do to prevent some of the osteoporosis and other side effects associated with hormone therapy.

Q. In your opinion, what is the best PSA number to consider starting hormones?

A. There is no magic number. I rarely, if ever, start below 10, doubling time or rapidly doubling in less than six months, I would start. I take it very conservatively and start them even as high as 22, depending on how rapidly it's growing. Also checking a bone scan on a regular basis, if you're not going to start.

Q. What about calcium? Should that be part of my regimen?

A. It's slightly out of my area of expertise but I listen to the people who are experts and they say that probably we emphasized too much on calcium in the past. Vitamin D is certainly not part of a normal diet, because we don't get as much sunlight in Canada, so I tell people that if you take vitamin D, 1,000 I.U., and two yoghurts a day and a glass of milk, you don't need anything else. The vitamin D I recommend is D-Drops. It's the cheapest, that's why you'll find it in the back of the store. Just take one drop a day, that's a 1,000 I.U. a day and you get a three or four month's supply for $14.00.

Prostate Cancer Canada - Newmarket

Newmarket, Ontario. 905-895-2263

www.newmarketprostatecancer.com

a member of the Prostate Cancer Canada Network

Assisted by the Canadian Cancer Society
Holland River Unit
905-830-0447

Your Executive

Doug Bowers, *May host*,	905-841-2759
Phil Mahon, *Secretary*,	905-473-2688
Walt Klywak, *Communications*,	905-895-1975
Jane & Frank Kennedy, *Treasurer and Newsletter*,	905-895-2263
Ulli Baumhard, *Greeter*,	905-478-8843
Pat & Ron Stevenson, *Greeters*,	905-836-1701
Dan Ho, *Photos & Membership*,	416-953-8889
Doug Bowers, *Member at large*,	905-841-2759
Doug Armstrong, *Website*,	905-778-0028