Prostatepedia[1]

[1]expert insight + advice

Heart Health + Prostate Cancer

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In this issue....

This issue is devoted to cardiovascular risk in prostate cancer patients. It turns out that the relationship is complex. Men with cardiovascular disease have a higher incidence of prostate cancer. This may, in part, be due to an impact of elevated cholesterol on prostate cancer progression. However, other factors may also be involved. For example, obesity is associated with an increased risk of cardiovascular disease and with progression of prostate cancer. Similarly, a diet rich in calories and meat is associated with an increase in insulin like growth factor 1 and this hormone has been liked to prostate cancer progression.

Removal of androgens, such as testosterone and dihydrotestosterone, plays a central role in the treatment of prostate cancer. In turn, low testosterone exacerbates insulin resistance, diabetes, visceral obesity and hypertension—known risk factors for cardiovascular disease.

In this issue, Dr. Pedro Barata from Tulane University gives us an overview of the issues at stake when we discuss prostate cancer and cardiovascular disease.

Dr. Michael Freeman from Cedars-Sinai discusses the evidence that cholesterol might drive progression in prostate cancer and the possibility that lowering cholesterol with statins might have a therapeutic impact. One of the more interesting observations he discusses is that certain gene expression patterns might lead to a increase or decrease in sensitivity to cholesterol levels.

Dr. Matthew Roe, a well known cardiologist from Duke University's Clinical Research Institute (DCRI), speaks about the PRONOUNCE clinical trial he's running. PRONOUNCE compares the cardiovascular safety of Firmagon (degarelix) versus Lupron (leuprolide) in men with advanced prostate caner.

Dr. Darryl Leong from Canada's McMaster University talks about his RADICAL-PC clinical trial, which evaluates the effectiveness of modifying cardiovascular and lifestyle risk factors in men who've just been diagnosed with prostate cancer.

Finally, Dr. Christina M. Dieli-Conwright talks about her clinical trial evaluating a 16-week program of cardiovascular and strength exercises in men with prostate cancer.

Charles E. Myers, Jr., MD Pp1

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Pedro Barata, MD
Cardiovascular Disease + Prostate Cancer

Dr. Pedro Barata is an Assistant Professor of Medicine at the Tulane Cancer Center. He's keenly interested in genitourinary tumors with a particular focus on clinical trials.

Prostatepedia spoke with him recently about the intersection between cardiovascular disease and prostate cancer.

Why did you become a doctor? And what has kept you interested?

Dr. Pedro Barata: I'm Portuguese and lived in Portugal for a long period of my life. Since I was young, I've been fascinated by medicine and research, and in particular, clinical research with patients. I remember thinking about how to help them. I'm not a lab guy, and I don't enjoy routine. I love seeing patients.

One of the reasons I chose medical oncology is because the field changes in such dramatic ways that we have no routine. Whatever I'm offering a patient today as the best standard of care won't be the best standard of care in a short period of time. That evolving landscape is a huge attraction to me. It really pushes me to read more, study, and investigate to be on top of things. That's the reason why I moved to the United States. Years ago, I trained at the Cleveland Clinic and MD Anderson, in the Departments of genitourinary (GU) tumors and clinical trials. When I was in the United States the first time, I soon realized that for me to be directly involved in research with patients and clinical trials, I needed to be in a place where those resources were available—otherwise, you cannot make it happen. So when I got the invite to come back to Cleveland for GU in 2014, I accepted.

I've been working for the last couple of years in solid tumors, with a focus on prostate, kidney, and bladder cancers. I design clinical trials and enroll patients in clinical trials for those cancers. I offer patients alternatives to the standard of care with a hope that some of these studies prove to be better, and so we move the science forward.

Why GU cancer as opposed to lung cancer or something else?

Dr. Barata: Prostate cancer has a great prognosis, so you establish a long relationship with these patients. It requires a multidisciplinary approach, which is something that attracts me a lot. You engage with urologists, radiologists, pathologists, radiation oncologists, and many others, which I also like. It's an area where you have a lot of opportunities to improve outcomes for patients.

There's so much more we can do in bladder and kidney cancers—and still in prostate—to improve the quality of life and the clinical outcomes of these patients. Those are areas where I could make a difference as a physician and a researcher. I'm not sure that's unique of GU tumors. But I don't have a personal motive to work in GU other than interest and enjoyment working with these patients and trying to help them.

Why do we even talk about cardiovascular disease when it comes to prostate cancer? It doesn't come up with lung cancer, so why does it in prostate?

Dr. Barata: When we think about cardiovascular events, it's actually a growing topic in this field. As treatments get better and better, patients live longer. Some develop cardiovascular events because they just live long enough to experience those long-term toxicities.

In regard to prostate cancer, it's usually in relation with hormonal therapy. For context, prostate cancer is a hormonally driven disease, and so its tumor growth depends on androgens. We've been using surgical castration or androgen deprivation therapy (ADT) to treat men with prostate cancer for several decades. We have been doing this to treat prostate cancer since the guys who discovered this got a Nobel Prize for it in the 60s. There's a clearer connection between cardiovascular disease and ADT.

Explanations for this increased risk include metabolic changes, such as hyperglycemia, or dyslipidemia, and factors in relation with arteriosclerosis. This has been an ongoing discussion, to determine why ADT is correlated with increased risk for a cardiovascular event and what we can do to prevent that. We use ADT in localized disease

> *"Hormonal manipulations give an increased risk for cardiovascular events."*

combined with radiation therapy. We use it in the biochemical recurrence space. We use it in the advanced setting. And we also have other therapies called novel androgen inhibitors, such as abiraterone or enzalutamide, to explore this pathway. All of these hormonal manipulations give an increased risk for cardiovascular events.

On the other hand, there's radiation, which is not a strong risk factor in prostate. In the majority of the cases, we end up not irradiating the chest, and so you don't have an increased risk for cardiovascular events as compared with lung cancer or breast cancer where radiation is given to the chest, especially to the left side where the heart is.

So, the risk for cardiovascular disease is mainly in ADT, novel androgen therapies, androgen pathway inhibitors, and chemotherapy to a much lesser extent.

What would you say to a man who's reading this and doesn't already have preexisting cardiovascular disease but has been prescribed ADT?

Dr. Barata: The risk is different depending on the patient. It is different when you have someone who already has preexisting cardiovascular risk factors such as high blood pressure or diabetes, for instance. Because we need to use ADT to suppress testosterone levels, the advice is always to go back and control cardiovascular risk factors in the best way possible. That usually includes getting the primary care physician involved in the care. He should have good blood pressure control, good diabetic or glycemic control, and he should focus on diet and exercise. Those are the factors that we can act on, and we can reduce or minimize the increased risks caused by treatment.

So you could address things as they come up?

Dr. Barata: Exactly. In the clinic on a day-to-day basis, apart from talking about prostate cancer, we talk about which risk factors are present, which are not, and what we need to pay attention to. We usually talk about these five things: ADT, diet, bone health, exercise, and good control of cardiovascular factors.

Every time I see a patient who is at moderate or high risk for cardiovascular events, I usually engage a cardiologist with a focus on oncology. They calculate the risk in a more objective manner. When we are concerned about the treatments we're considering and their cardiovascular risks, involving a cardio-oncologist is a good way of making sure we don't miss anything.

> *"We usually talk about these five things: ADT, diet, bone health, exercise, and good control of cardiovascular factors."*

There are some data, which are not very strong, that suggest that an antagonist has a lower risk compared with an agonist in causing cardiovascular events. This is not settled yet, but there is a large Phase III trial going on to answer the question. Right now, we don't have a preference. If it turns out that an antagonist correlates with the lower risk for cardiovascular events, then we'll change our practice, and we'll start using the antagonist as the treatment of choice.

Do you know who's running that trial?

Dr. Barata: The trial is called PRONOUNCE. The collaborators of the study are Memorial Sloan Kettering and Duke Institute, and it's sponsored by a pharma company. It's still open. It's a trial comparing the cardiovascular safety of degarelix, which is the LHRH antagonist, versus leuprolide, which is the LHRH agonist, in patients with advanced prostate

"It's important that survivorship programs for prostate cancer be mindful of cardiovascular events."

cancer and cardiovascular disease. (See page 12 for a discussion with Dr. Matthew Roe about this trial.)

I predict it might be closed soon because it's been open to accrual since 2016. We hope to have a result in the next 24 months.

What about after ADT treatment?

Dr. Barata: Fortunately, we cure a lot of patients with prostate cancer. Every time we deliver a treatment that cures but increases the risk for cardiac events, we should let the patient know that their risk doesn't go away.

Because we deliver hormones for a short period of time for prostate cancer, that's not as important as it is for other cancers. In testicular cancer, for instance, we follow patients to make sure that we have cardiovascular risk factors under control. So it's important that survivorship programs for prostate cancer be mindful of cardiovascular events.

Does the impact that ADT has on prostate cancer last even after the ADT has been stopped?

Dr. Barata: We don't know. In the localized setting, the duration of ADT is relatively short. For instance, if you have intermediate risk prostate cancer, you usually deliver six months of hormones, and if you have a high-risk disease, you treat them for two to three years. We have no long-term data showing the long-term impact on cardiovascular events for patients treated with three years of hormones, where you suppress testosterone for three years.

"What can you do to prevent or minimize cardiovascular events in the future?"

We do know that, if you have advanced prostate cancer, you are usually in a long-term ADT, meaning continuous suppression, and that can last for five or more years. That's where there's more data.

If a person has diabetes or a prior history of cardiovascular problems, their primary care physician should be engaged to make sure that, even though we are done with treatments, we are still paying attention to preventable cardiovascular risk factors, like blood pressure, exercise, and diet.

Do you have any advice for men either going into prostate cancer treatment or already undergoing treatment?

Dr. Barata: There's frequent toxicity in patients diagnosed with GU tumors in general, and prostate cancer is more associated with ADT. Ask your treating physician about your specific risks. What can you do to prevent or minimize cardiovascular events in the future? Is there a role for a cardio-oncologist, a cardiologist with a focus on oncology, on your healthcare team? Pp

Michael Freeman, PhD
Cholesterol, Statins + Prostate Cancer

Dr. Michael Freeman is the Director of both the Division of Cancer Biology and Therapeutics Research in the Department of Biomedical Sciences and the Division of Basic Science Research in the Department of Surgery at Cedars-Sinai in Los Angeles.

Much of his work and the work of his laboratory at Cedars-Sinai focuses on prostate cancer progression.

Prostatepedia spoke with him recently about cholesterol, statins, and prostate cancer.

Why did you initially become involved in cancer research, and what has kept you there over the years?

Dr. Freeman: I'm a research scientist with a Doctor of Philosophy, but I'm not a medical doctor. I have done research full-time since 1979, when I became interested in it as a career in college. A professor had a big impact on my life, and I worked with him for about two years before graduate school.

My PhD is in molecular biology, and there wasn't any real medicine in my curriculum or environment, so I had a pretty basic science upbringing. Then, I did a post-doctorate fellowship at MD Anderson Cancer Center, which was a huge change in environment.

My PhD was at the University of Colorado, Boulder. Boulder is a college town. The medical component of the University of Colorado is in Denver, and so I was isolated from any medicine. But in Texas, I was thrown into this giant medical center, an enormous cancer center. There, I learned what cancer was, and I learned how to do cancer research. I have worked on prostate cancer as one of several research areas since the 1980s, and in these last eight years of my career, I've done almost only cancer research.

What is it about prostate cancer, among the other types of cancer, that fascinates you?

Dr. Freeman: Prostate cancer is highly curable. Cure rates for localized disease are almost 100 percent. Yet, it's a lethal disease. You have about 25,000 deaths in the United States per year from prostate cancer. It has highly morbid disease progression. Your skeleton basically dissolves from bone metastases while you're alive; it's very painful. In the last few years, we've been wrestling with the difference between the lethal form of prostate cancer and the relatively indolent form of prostate cancer that can grow slowly but won't kill you.

Under the microscope, these tumors can look very similar, or even identical. What's going on biologically is hidden: we have to use molecular methods to pull those characteristics out, to understand what they are. It's a fascinating and complicated biological problem.

What do we know already about cholesterol and prostate cancer? What do we still not know?

Dr. Freeman: There are two lines of evidence about cholesterol and prostate cancer. One comes from the epidemiology literature, which has established a link between cholesterol-lowering drugs, which are widely prescribed, and prostate cancer risk. This is quite a voluminous literature that goes back into the early 2000s. There were some important studies in the mid-2000s and a little later that tried to nail down this link.

In 2019, it's clear that there's a link between use of cholesterol-lowering drugs—mostly statins—and prostate cancer. Statins are drugs that inhibit an enzyme called HMG-CoA reductase, which is involved in a variety of biosynthetic processes, but is an enzyme for cholesterol biosynthesis, mostly in the liver. When this enzyme is suppressed, you lower circulating concentrations of cholesterol and other types of lipids, and you can monitor these accurately using blood tests.

"In some individuals, cholesterol can drive prostate cancer."

It's been known for a long time that these types of drugs can substantially improve cardiac health and can lower the risk of heart disease. There are many people who have taken these drugs over a long period of time, and you can do epidemiologic studies to look at their rate of cancer of various types. Looking at that literature, there seems to be a signal. If you do meta-analyses (these large composite studies in which a whole variety of papers are analyzed, grouped together, and then the data are analyzed together) it looks like lowering cholesterol for prostate cancer is protective. That said, there's still a lot of controversy about this literature.

The controversy comes from inconsistent findings in different studies, the fact that these statin drugs have different potencies, they're not all the same, and other elements, such as ethnicity. Ethnicity seems an important component in whether or not someone is likely to have an aggressive tumor or will respond to certain types of either therapy or preventive strategies. Almost nothing is known about that. So, you have these confounding variables that may obscure this statin drug relationship.

That's one line of investigation: these cholesterol-lowering drugs may be protective for prostate cancer.

You're talking about the relationship between these cholesterol-lowering drugs and prostate cancer risk, but what if you lower cholesterol with other means?

Dr. Freeman: You can do that. There are drugs that operate by other mechanisms and lower cholesterol but are not statins. These other types of therapies are relatively new, so the problem is that there are not enough of those patients to even do a study yet. Many of the studies that have been done are retrospective studies, which may have lots of patients but are not specifically focused on prostate cancer.

What's the second line of inquiry about cholesterol and prostate cancer?

Dr. Freeman: The second line is pre-clinical studies, which have done various things like lower circulating cholesterol in mice carrying human tumors. Studies of cholesterol, effects of taking away cholesterol, adding back cholesterol in tumor cells in cultured media in the laboratory, and various type of pre-clinical studies, which we and others have done, are more persuasive. You can have very controlled situations, take more precise measurements, and see interesting effects.

From those studies, it seems that the cholesterol molecule can drive prostate cancer growth under some conditions. I've summarized many papers in these remarks, but I would say that if you look at the literature collectively, including the population studies and the pre-clinical studies, it looks like, in some individuals, cholesterol can drive prostate cancer.

Some patients will read this and wonder whether they should make efforts to lower their cholesterol in hopes of impacting their prostate cancer. Should they diet and make lifestyle changes? Should they consider a statin, even if they're not already prescribed it for pre-existing cardiovascular disease?

Dr. Freeman: I don't think anyone would make a recommendation specifically about prostate cancer. Lowering cholesterol has all sorts of positive effects that can potentially extend your life. The same is true with certain types of lifestyle interventions like exercise, which can lower cholesterol. The problem with some of these recommendations is that they may have ultimately nothing in mechanistic terms to do with prostate cancer. But they are good for you and could even suppress the rate of progression of your disease, and it could happen a variety of ways.

For example, somebody who is obese has higher risk for cancer progression in many instances, simply because their biology differs from the biology of a lean person. And that includes things like cytokines. Fat is a major source of potent bioactive molecules that end up in the circulation and go everywhere in the body. They can be cancer promoting, and we know many mechanisms that can be triggered by things like that. If you reduce the adiposity in your body,

in most instances, it will have a health benefit, whether or not it's specifically directed towards prostate cancer.

But I don't think anyone would recommend taking a statin specifically to suppress prostate cancer.

Right. So the hope is that, in men who are already prescribed statins to treat cardiovascular disease, it might have some impact on their cancer?

Dr. Freeman: Yes, or just their general health.

What current clinical trials look at statins in prostate cancer?

Dr. Freeman: There's one at Cedars-Sinai and another in Toronto. These are trials specifically designed to test for biological effects that may be consistent with tumor suppression in men who are getting prostate cancer surgery, so they're having a prostatectomy. They'll go on a statin prior to surgery for a number of weeks, and then once the prostate tissue is taken out, it will be analyzed for things like cell proliferation or prostate cancer cell death. These pre-prostatectomy trials are ways to determine whether or not statins have biological effects on the prostate specifically.

It seems provocative subject matter. Considering how many people are already on statins and how many people have prostate cancer, why do you think there aren't more trials looking at the relationship?

Dr. Freeman: Because endpoints in prostate cancer are very difficult. In this particular case, you'd be looking at rates of progression, and it's difficult to measure progression rates in prostate cancer because of the long timelines.

The other problem is the indices that people use to measure progression. Some of them are considered problematic, and that's even true with PSA rise. That's called biochemical failure. You have treatment for prostate cancer. You remove all the prostate tissue, prostate specific antigen, which is mostly expressed in the prostate. That secreted protein is under the control of androgens, so if there's hormone suppression, or if the prostate is removed, that circulating level of PSA goes down to basically zero.

"Lowering cholesterol has all sorts of positive effects that can potentially extend your life."

Then if the prostate cancer comes back, the concept is you can follow rate of progression of the emergent disease by doing the blood tests that measure PSA. The problem is that there are lots of confounders in this biochemical failure as an endpoint, and using any other strategy makes it very difficult to measure progression quantitatively. What you want to do with a statin anyway is suppress the rate at which the tumor comes back after therapy, so you're looking at timelines of years. It's just very difficult to design those trials prospectively.

If you're trying to design a trial that's financially supported and the endpoints are going to be five to ten years down the road, it's almost impossible to do those

"Cholesterol is a biochemical precursor for male hormones."

kinds of experiments. That's why people do the pre-prostatectomy. For these sorts of things that are really chemo-preventive, people will design these pre-prostatectomy trials. Even there, the metrics are not great for determining whether or not there's effect on the cancer.

Any other thoughts about cholesterol and prostate cancer?

Dr. Freeman: We are working on this interesting biology now. Cholesterol is a biochemical precursor for male hormones, for androgens. There's some kind of biochemical relationship between androgens and cholesterol that we can see in genomics data from large numbers of subjects. Androgens are major drivers of prostate cancer, which has been known for decades. The question is: what's the relationship between cholesterol and the androgen biochemical axis?

There is quite a lot of data available now in the public domain, so people can analyze it themselves. And we look at large data sets that involve whole genome expression analyses of human prostate cancer. What we see is that, in certain subtypes of prostate cancer, there's a strong correlation between genes that specify processes within the broad context of cholesterol metabolism and androgen signaling. Many or most of the genes that are downstream from androgen action are known, and so we can compare quantitatively this androgen gene signature with the cholesterol homeostasis metabolism signature.

What you see in some patients is an amazing positive correlation that suggests that there is a relationship between cholesterol and metabolism and androgen action. But you only see that in some patients. That suggests that if we knew who those patients were, we could find them using some sort of a molecular analysis approach. We could then suppress cholesterol in those patients, and we would see effects. That is the state of the research now.

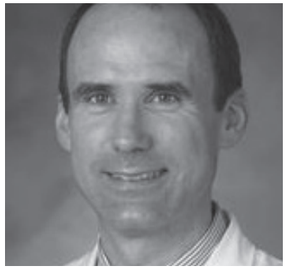
This relationship between androgen action, as measured at the RNA expression level across the whole genome, and cholesterol metabolism, which we see in the data, is very strong. We don't understand that relationship, but it suggests that if you suppress cholesterol, you would see preventive effects, or maybe even therapeutic effects in some patients.

That's fascinating. Are you now looking at the genomics of those who respond?

Dr. Freeman: We're trying to. We are writing papers and grants around this idea, so we're very interested. It suggests that you really need population scale data in order to do these things. You have to be able to separate patients into subtypes.

Not everybody has the same prostate cancer. It might look the same in the microscope, but at the molecular level, it's not the same. We don't understand the molecular basis yet. Pp1

Matthew Roe, MD, MHS
Firmagon Versus Lupron



Dr. Matthew Roe is a Professor of Medicine at Duke University's Clinical Research Institute (DCRI), the Faculty Director of the Global Outcomes Commercial MegaTrials program, and the Director of their Fellowship Program. (The DCRI's databank is the world's oldest and largest cardiovascular database.)

He has participated in the leadership and conduct of numerous clinical trials focused on therapies for acute coronary syndromes and chronic cardiovascular disease. He is keenly interested in clinical trials' operational conduct as well as in national and global academic collaborations.

Prostatepedia spoke with him recently about a clinical trial he's leading that looks at the cardiovascular safety of Firmagon (degarelix) versus Lupron (leuprolide) in men with prostate cancer.

Why did you become a doctor? What is it about medicine that has kept you interested?

Dr. Matthew Roe: I became a physician because I was very interested in the biological sciences. I learned that I very much enjoyed working with people; that is patients and their families. I had an opportunity, as an undergraduate student at the University of Virginia, to volunteer in the hospital on the pediatric ward and actually spend time with young patients and their families who were hospitalized for various conditions. I really enjoyed that interaction and I enjoyed helping people.

"Is there is a lower cardiovascular risk with Firmagon (degarelix) versus Lupron (leuprolide)?"

The two seemed to be a natural fit. I was able to meet a number of physicians who were good role models. I felt like it was a worthwhile and challenging profession and one that would never be static. It would always be dynamic and always pose challenges and always be interesting and variable throughout my career. I've been in practice for 20 years and I can say that's definitely the case. Every day is different and new, but it's rewarding and challenging. I've been able to not only do clinical care, but also participate in clinical research activities. It's very important to me to be able to help understand what the best treatments are for our patients and help improve how we care for them. That's what clinical research is all about.

What's the thinking behind your clinical trial comparing cardiovascular safety of Firmagon (degarelix) versus Lupron (leuprolide) in patients?

Dr. Roe: Years ago, a number of studies were done that showed a potential signal for increased cardiovascular event risk among patients with known cardiovascular disease who were receiving androgen deprivation therapy, the standard of which is Lupron (leuprolide). Eventually, there was a document released by professional societies, including cardiology professional societies and urology professional societies and a black-box warning on the label of that drug, that there is the potential that patients with known cardiovascular disease who receive this therapy could have an increase in cardiovascular risk. That therapy is used to treat advanced prostate cancer and has known benefits there. These professional societies were trying to set up a shared decision-making model with prostate cancer patients and their physicians to better understand if this therapy should be used, and if so, how should they monitor it.

Then Firmagon (degarelix) was developed as a different type of androgen deprivation therapy with a different target, having similar efficacy in treating prostate cancer. Some post-hoc analyses suggested that patients who receive Firmagon (degarelix) might have a lower risk of cardiovascular events when they have known prior cardiovascular disease while receiving this drug as treatment for prostate cancer. All these studies that were done were retrospective studies that weren't meant to answer that question.

The trial we're conducting, the PRONOUNCE Study, was designed as a prospective rigorous randomized trial to compare those two treatments among patients with prostate cancer, to understand if there is a lower cardiovascular risk with Firmagon (degarelix) versus Lupron (leuprolide).

What can a patient expect to happen during the trial?

Dr. Roe: A number of sites in the United States and other countries are participating. In those sites, urologists or oncologists who treat patients with prostate cancer are evaluating their patient population whom they're considering treating with androgen deprivation therapy. If they meet their eligibility criteria for the trial, they discuss the trial with them.

If the patient is eligible and he chooses to participate, then he is randomly allocated to receive Firmagon (degarelix) or Lupron (leuprolide) for 12 months. The therapy is provided to him as a study participant. He will be seen every month during the

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"A number of sites in the United States and other countries are participating."

study to do a check in and assess whether or not he has experienced a cardiovascular event and to optimize his background treatment therapy for both prostate cancer and cardiovascular disease.

I work at the Duke Clinical Research Institute. We're the academic coordinating center, working with the sponsor Ferring Pharmaceuticals to help design, run, and conduct the study. This is a collaboration between academic experts and the sponsor. We have a steering committee of academic experts—cardiologists like myself, urologists, and prostate cancer oncologists to work together to conduct this study.

Are there any specific eligibility criteria that you'd like to call attention to?

Dr. Roe: Yes. We are looking for patients with prostate cancer who meet the criteria to receive androgen deprivation therapy. I'm not going to go into the exact details, but the trial is for those eligible for advanced prostate cancer treatment. These would be people who would not be receiving a prostatectomy or radiotherapy treatment. These patients have to have a known history of prior cardiovascular disease, which we confirm. We work with the study sites to implement that confirmation, because urologists and oncologists treating patients with prostate cancer aren't really experts in cardiovascular disease. We work with them to ensure that they're meeting those criteria and that they're treating patients appropriately. In many cases, a cardiologist will work with the site investigator, who is an urologist or an oncologist, to help conduct the study.

"This is a collaboration between academic experts and the sponsor."

I'm sure there are quite a few men with advanced prostate cancer who also have cardiovascular disease.

Dr. Roe: Yes. It's estimated that about 35-40 percent of men with advanced prostate cancer will have a known history of cardiovascular disease, partly because both conditions are common in older age. That is one of the strongest risk factors for both prostate cancer and heart disease, so we see the convergence of those two conditions.

If someone reading this is interested, who should he contact?

Dr. Roe: We do have at least 30 or so sites in the United States. If someone is interested, he can contact me directly and then I can put him in touch with the right people. One of the challenges is that only a certain number of physicians who treat patients with prostate cancer would be interested in participating and being investigators for the trial, so matching them with patients around the country is always a challenge. We are happy to help patients who are interested in participating have that opportunity, even if their local doctor may not be the one who's the investigator.

Is there any fee for patients to participate?

Dr. Roe: No. They receive reimbursement for their travel to come to and from the clinic for their visits. They receive the therapy that they're getting, Firmagon (degarelix) or Lupron (leuprolide), for free. There are no costs for the patient; they just have to volunteer their time. We recognize that and we share information with the patient. At end of the day, we will share the information from the study directly with the study participants, to help them understand their contribution and what it means going forward. We overtly honor the volunteerism and altruism of the patients.

Is there anything else you'd like patients to know, either about this trial in particular or the context in which it occurs?

Dr. Roe: If a patient who has advanced prostate cancer and known cardiovascular disease is being considered for androgen deprivation therapy, it is important that he speak with his cardiologist. (Presumably, both a cardiologist or cardiovascular specialist and an urologist or oncologist would treat him.) He needs to ensure that all the providers have a discussion about what the best and safest treatment would be before therapy begins. Obviously, this trial is not completed yet so we don't have any answers. In the meantime, it is certainly in the patient's best interest to ensure that his providers are communicating and trying to jointly determine the right approach. Pp[1]

Clinical Trial: Cardiovascular + Lifestyle Interventions

Dr. Darryl Leong is a cardiologist and Assistant Professor in Medicine at Canada's McMaster University. He's particularly interested in the prevention, identification, and management of cardiovascular disease in those with complex diseases. He is also leading the development of a clinical research program for the evaluation and treatment of cardiovascular disease in patients with cancer at Juravinski Hospital.

Prostatepedia spoke with him about the RADICAL-PC clinical trial, which is a randomized intervention of cardiovascular and lifestyle risk factors in prostate cancer patients.

Why did you become a doctor?

Dr. Leong: Within a generation, our society has added 20 years of lifespan. This is consistent whether it's in wealthy countries like the United States and Canada or in developing countries. We have been really successful in a short time at prolonging people's lives, and so the science that went behind that was really interesting to me.

When you look at the history of the world, in hundreds of millions of years, I don't think any species has seen such a lengthening in their life expectancy in such a short period of time. I hope to build on that with our research and help to improve not just life expectancy but also people's quality of life.

Would you tell us about the thinking behind your clinical trial?

Dr. Leong: We read some papers that came from the United States and Europe that suggest two things. First, men with prostate cancer seem to have quite a high risk of developing cardiovascular disease, heart attacks, and strokes during the course of their follow-up. Second, there might be a link between (hormonal) androgen deprivation therapy (ADT) and the occurrence of these sorts of cardiovascular events. So, our thoughts turned to cardiovascular disease and prostate cancer.

We proposed a study to the charitable organization Prostate Cancer Canada (http://www.prostatecancer.ca/) that supports research to understand why this link exists. We were fortunate enough that Prostate Cancer Canada agreed to fund our proposal, and so that's how we came to study over 2,000 men with prostate cancer in Canada.

We'd like to expand this research internationally because we know that what happens in one country may not necessarily reflect what's happening in another country. We have ongoing efforts to try to expand.

> *"Men with prostate cancer seem to have quite a high risk of developing cardiovascular disease, heart attacks, and strokes during the course of their follow-up."*

What will you be doing in the study? Should a man reading elect to participate what can he expect to happen?

Dr. Leong: One level of involvement, which we would ask of anyone who is interested in being involved in the study, is that we collect information about you, and we follow up with you over time. We hope that period of time will be at least another three years. If we are successful in getting more funding, we'd like to make it long term.

At the beginning, we collect information about health, cardiovascular disease, and risk factors that people have today, as well as information about physical characteristics, muscle strength, fitness, and a range of factors like that. Then we follow up with folks over the years to see if people develop cardiovascular disease or heart attacks and strokes and what predisposes people to these complications.

For more information …

Contact the RADICAL-PC study coordinator, Sarah Karampatos, at Sarah.Karampatos@phri.ca

In addition to monitoring for cardiovascular disease, and because this is an opportunity to see whether we can make a difference to the cardiovascular disease rates in men with prostate cancer, we decided that people within the RADICAL-PC who give consent would be randomly allocated into one of two groups.

One group would receive usual care. Their medical care would not be changed at all. They would continue to see their general practitioner and their cancer specialist. The other group would be allocated to see a cardiologist on top of their usual care. The cardiologist would be instructed to provide very focused interventions to reduce cardiovascular risk. So, this is a trial built into the RADICAL-PC trial to see whether or not we can reduce cardiovascular events in these men.

Are there any specific eligibility criteria?

Dr. Leong: The criteria are simple. All we ask is that they're over 45 years of age, and that either their prostate cancer has been diagnosed within the past year, or they've started hormonal therapy within the past six months or have a plan to start it in the next month.

If someone reading this is interested, whom should he contact?

Dr. Leong: Men within Canada should contact us, and we can put them in touch with the nearest site that's involved in this research.

Can people participate from afar?

Dr. Leong: At the moment, we are restricted by our funding rules to recruit people within Canada. That's something we'd like to change, and we're working with potential collaborators for funding in a number of other countries.

The key is that initial visit. After that, we have follow-up visits to collect information about people's progress, but a lot of that can be done over the telephone, if distance is a problem. That first face-to-face visit to measure things like blood pressure and heart rate is the most critical.

But it really would be helpful to hear from men in other countries because funding agencies are interested in what patients want and what's important to them.

If we come to funding agencies in the United States or Europe and show them patient testimonials saying that this study is something they find important, that's very compelling. So, absolutely, please contact us.

For more information …

About Dr. Leong's other clinical research for men with prostate cancer, contact him directly at radicalpc@phri.ca

Any final thoughts for men about prostate cancer and cardiovascular disease?

Dr. Leong: For many men with prostate cancer, it is a lengthy disease process. It's not something that is imminently life threatening for most, but it's something that, if not adequately treated, causes an important risk. Because many men with prostate cancer will have life expectancies of years, it's a good opportunity to address other health issues, which are just as likely as the cancer to cause harm or kill.

> *"The cardiologist would be instructed to provide very focused interventions to reduce cardiovascular risk."*

We have ongoing research not just in cardiovascular disease but also in things like depression, physical fitness, and muscle strength and function in men with prostate cancer. And these are going to be really important aspects for quality of life. Pp

Clinical Trial: Exercise For Metabolic Dysregulation

Dr. Dieli-Conwright is an Assistant Professor of Research in the University of Southern California's Division of Biokinesiology and Physical Therapy.

She's particularly interested in understanding physiologic mechanisms and designing exercise interventions for cancer patients.

Prostatepedia spoke with her about her clinical trial.

How did you come to study exercise in cancer patients?

Dr. Dieli-Conwright: : It came about pretty early on when I was a graduate student. I started to read more and more literature that was published about the association between how much someone exercised in their lifetime affected their cancer risk. Particularly back then, it was applied mainly to the breast cancer setting and was mostly epidemiological work.

Once I saw that, I thought, well, I'm an exercise physiologist and exercise could be a way to intervene. More work started to come out that also suggested that if you exercised it could alter your risk for cancer recurrence. I started to think of ways that we could apply exercise to this population. At that time, it was a relatively newer field and is now generally called exercise oncology: we apply the field of exercise to a cancer setting. This term usually refers to patients who have already been diagnosed, but that can also include people who may be are at a higher risk for developing cancer.

I did my postdoctoral training at City of Hope, which is a cancer center in Southern California. That was where I got to see firsthand what the patients were experiencing as they were undergoing chemotherapy and radiation. I started to hear anecdotal feedback from the patients about how treatment was making them feel. What was changing with their bodies and with their behaviors? Then I just started to derive exercise questions related to that.

What is the thinking behind your clinical trial?

Dr. Dieli-Conwright: This study spawned from my interest in the side effects and changes that patients were experiencing as they underwent treatment. For some of the more prevalent cancers like breast, prostate, and colorectal cancer, there is literature to provide evidence that individuals are experiencing what I broadly call metabolic dysregulation, which encompasses things like gaining weight, insulin resistance, elevated inflammation, and elevated blood pressure.

Whether they have metabolic dysregulation before diagnosis or whether it develops during treatment, they are at higher risk for experiencing diseases like heart disease, diabetes, and obesity.

In prostate cancer in particular, when men are prescribed androgen deprivation therapy, there are side effects to that therapy that lead to metabolic dysregulation.

If you look at individuals who exercise who have not had cancer, we know that exercise can successfully offset metabolic dysregulation. It can improve insulin resistance. It can reduce body composition changes, etc. We wanted to apply exercise to this particular population so that these patients may also experience the benefits of exercise.

If a man who's reading this ends up participating, what can he expect to happen step by step?

Dr. Dieli-Conwright: This is a randomized controlled trial. Individuals will be randomized to either the exercise group, and receive a 16-week, 3 times a week exercise program immediately, or the delayed controlled group. Everybody eventually gets the exercise program, but the "exercise group" gets it first. The delayed controlled group gets the program 16 weeks later.

We ask them to come to our facility, which is here at University of Southern California, to exercise. We pair them one-on-one with a certified cancer exercise trainer. They perform both aerobic and resistance exercises for about one hour every time they come. They perform the exercises in an interval circuit training, high-intensity manner. We've done that so that we can really challenge the metabolic systems for energy balance that have been shown to be more effective at targeting metabolic dysregulation as to opposed, for instance, just walking on a treadmill for 60 minutes.

We do a number of tests at the beginning, middle, and end of the 16 weeks. Those tests involve a blood draw so that we can measure glucose and insulin, as well as triglycerides, cholesterol, and markers of inflammation. We measure blood pressure, waist circumference, and body composition so how much muscle and fat the patients have. We also measure bone density. We do a battery of what we call physical function tests: how fast can the man climb upstairs? How fast can he walk six meters? How many times he can sit to stand? We do what we call a cardiopulmonary exercise test to test their maximal fitness and we do a series of strength tests to see how strong their muscles are.

We give them a packet of questionnaires about quality of life, fatigue, depression, and other cancer-related symptoms. We are measuring the whole gamut of health outcomes even though our main focus is on insulin resistance and metabolic dysregulation simply because that's the precursor to diabetes and heart disease.

We retest those measures at Week 8 and Week 16. We do follow participants after the 16-week period is over. Regardless of what group they were in, we check on them four months later to see how they're doing.

Are there any specific eligibility criteria that you want to call attention to?

Dr. Dieli-Conwright: The main thing is that they're over the age of 18 and that they have been on androgen deprivation therapy for the previous 16 weeks. That's just so that we can allow the medication to stabilize the hormones. We also look to see whether or not they have been exercising regularly. If they are highly trained from a fitness perspective, then they are not eligible, so we do actually look for people who are relatively sedentary who are not participating in a structured exercise program already. We do that because we are trying to reach out to people who may be at a higher need for these interventions.

Do you care if a man has had surgery or radiation for prostate cancer?

Dr. Dieli-Conwright: No, we do not, as long as the surgery or radiation is completed. If they're actively on radiation or actively on chemotherapy we would wait until that treatment is done. Often we get calls from patients who are very enthusiastic and eligible, but then tell us they're starting radiation next week. We have to wait until that treatment is over and they're cleared by their oncologist for exercise.

Is there anything else you'd like patients to know either about this trial in particular or about exercise for cancer patients in general?

Dr. Dieli-Conwright: We've had a number of patients participate already. It's been very successful. It's safe. It's feasible. Everybody's enjoyed the program. We've had very high compliance to date—almost 100%.

But it's a strong time requirement—3 times a week for 16 weeks—so I would just say that if anybody is interested, even if it's just a small amount, to contact us. We have very flexible scheduling times and can accommodate exercise almost 24/7. We have a large staff and a number of trainers who are eager to help. We try not to turn anybody away because of scheduling and try to work around work schedules if that's a concern.

We would love to take more patients. Pp

For more information …

Contact Dr. Christina Dieli-Conwright at 323-442-2905 or cdieli@pt.usc.edu

Clinical Trial: Metformin + Casodex (bicalutamide)

Dr. Marijo Bilusic is the director of the National Institutes of Health (NIH) Hematology Oncology Fellowship, and an Associate Research Physician in the Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute (NCI). He's keenly interested in tumor immunology and in developing prostate cancer treatments using novel target agents, therapeutic cancer vaccines, antibodies or immune modulations.

Prostatepedia spoke with him about a trial he's running that looks at men with prostate cancer on Casodex (bicalutamide) with or without metformin.

Why did you become a doctor in the first place?

Dr. Bilusic: When I was a student in primary school, I became very interested in biology and in trying to understand how the human body works. Medicine has fascinated me since I was six or seven. Later, my uncle was going through medical school, and I came across some of his textbooks of medicine, which sounded so appealing to me. I wanted to do what he did. I told my mom one day, "I'm going to be a doctor." And she said, "Okay. Do well in school, work hard, and things will come up."

Throughout primary school, biology was my favorite subject. I did my medical training in Croatia. That medical system is different from here because there's no college; everything's combined with medical school. After I graduated from medical school, I started a PhD, and then I came to the United States in 2002. I did my PhD in Physiological Genomics, followed by internal medicine residency, and then a medical oncology and hematology fellowship here at National Cancer Institute (NCI). After that, I joined the Fox Chase Cancer Center in Philadelphia, for about three and a half years. I was assistant professor (genitourinary medical oncology) there and ran several prostate cancer trials. And now I'm back here at NCI.

What it is about medicine and research that keeps you interested?

Dr. Bilusic: Oncology is sometimes very depressing. We are trying to extend life. The most exciting part is when you can help your patients, improve their symptoms and prolong life. Oncology is on the frontier of medicine. We are improving cancer treatments daily, making people live longer. We are curing many more people than before. Everybody used to be afraid of the word cancer. But now, things are changing. There are many new clinical trials and many new drugs being approved. Today, through our work and research, we are making huge steps forward.

It's becoming more of a chronic disease.

Dr. Bilusic: That's correct.

Would you walk us through the thinking behind your trial looking at Casodex (bicalutamide) with or without metformin?

Dr. Bilusic: A former prostate cancer patient of mine had had surgery and his prostate was removed. Then his PSA kept rising, and he was not very keen about hormonal therapy, which was recommended by other oncologists he'd seen before me. I met him, and we talked about what to do.

"We're just going to observe you for now," I said. "Try to exercise, lose some weight, and make healthy lifestyle changes. We'll see you back in three months, and we'll see what your PSA's doing."

In three months, he came back, and his PSA was 50 percent less than before. It went from 4 to 2. I was impressed. I asked him, "What did you do?"

"I followed your instructions."

"Lots of people follow my instructions," I said, "but I've never seen anybody have PSA decline just with exercise and diet change. Any other changes from the last time we met?"

"I've also been taking metformin," he said. "I read that metformin can help people with prostate cancer and asked my primary care physician to prescribe it, even though I was not diabetic." It's important to note that metformin is not something that we would recommend to prostate cancer patients outside of a clinical trial, yet. That's why we're running this study-to learn more about how metformin works and who it may work for.

I was surprised, and grew curious about a potential link. After that, I did a literature review. I found one population-based observational cohort study that included around 38,000 men with prostate cancer and diabetes from Ontario, Canada. Authors reported that metformin treatment was associated with decreased prostate cancer mortality: 24% reduction for each additional 6 months of metformin use while use of other antidiabetic medications did not significantly decrease mortality. This was a very interesting study. Two prospective studies tested metformin in non-diabetic patients with prostate cancer. First enrolled 42 patients with castration resistant prostate cancer who were treated with metformin, 1,000 mg twice daily. Two patients had ≥ 50% PSA decline and in 23 patients (52.3%) had a prolongation of PSA doubling time. Another study enrolled 24 men with newly diagnosed prostate

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For more information …

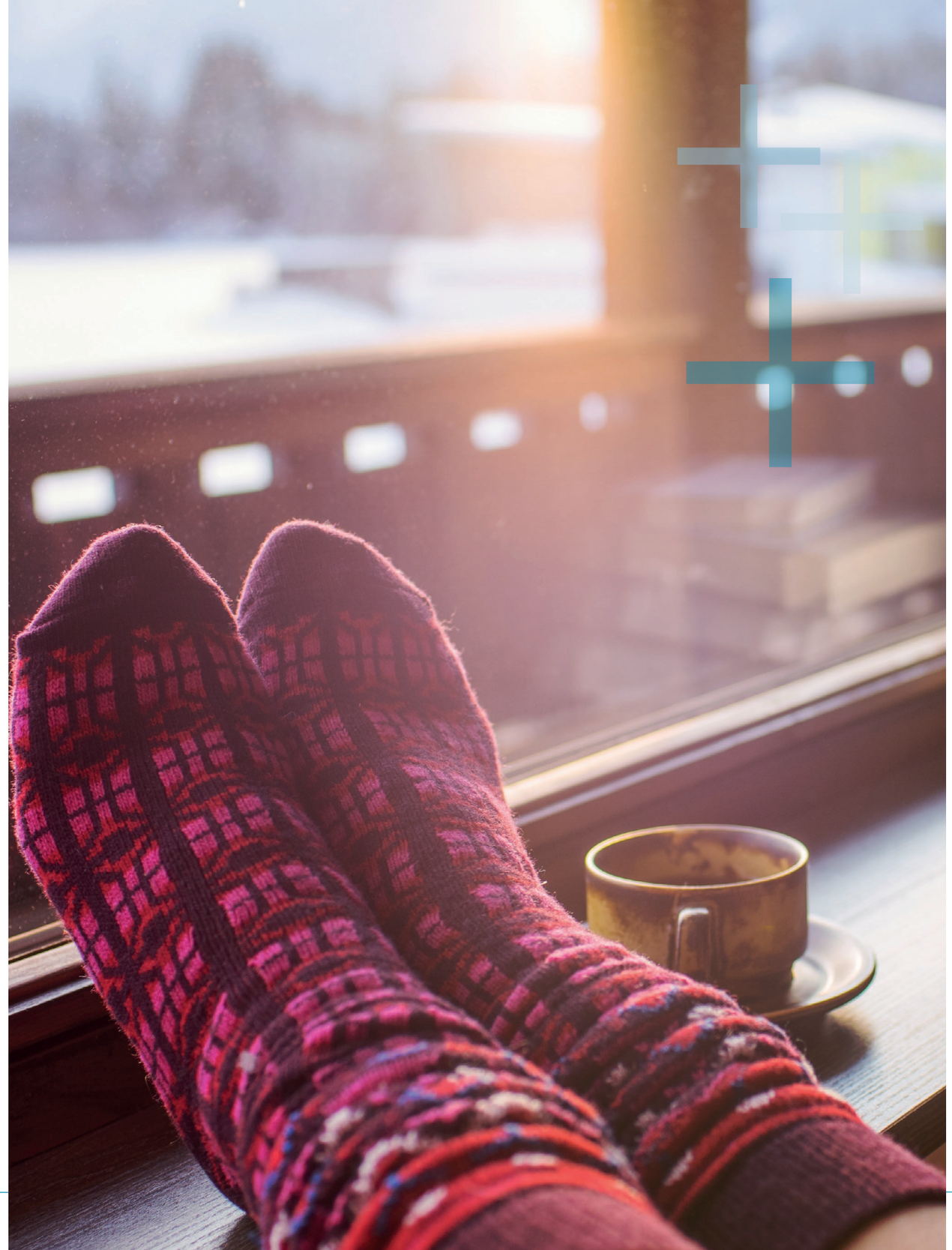
Dr. Marijo Bilusic at marijo.bilusic@nih.gov or Dr. Daniel M. Geynisman at daniel.geynisman@fccc.edu

cancer that were treated 500 mg of metformin three times a day before the surgery (neoadjuvant treatment). Metformin reduced Ki67 proliferation index by 29%, compared to the baseline biopsy, meaning that the cancer became less aggressive with metformin use of about four weeks. That was very interesting.

Nobody knows how metformin works, exactly. Some studies have shown metformin also could help patients with breast cancer and pancreatic cancer, and also observational studies have shown decreased risk of the incidence of cancer, suggesting that metformin can help prevent cancer.

Though we are still trying to understand how metformin works, we do know it's inexpensive and it's very safe. Instead of having a treatment of prostate cancer that costs more than $100,000, it would be great to have one that costs only a couple of dollars. We're not there yet, but we're hopeful that this trial and others like it will help us continue to learn more about how to best treat prostate cancer.

To learn more about when metformin may work, we came up with the study design to test metformin in combination with Casodex (bicalutamide), an FDA-approved agent for prostate cancer. We selected Casodex (bicalutamide) because testing of this combination using animal model showed the synergistic effect of Casodex (bicalutamide) and metformin. The side effects profile is much better than from Lupron (leuprolide), so we thought that would be a reasonable alternative for people who have biochemically recurrent prostate cancer with rapidly rising PSA.



What can patients expect to happen in the trial?

Dr. Bilusic: First, we have to make sure they're eligible. When they contact us, we determine if they have a biochemical recurrence, which we define as somebody who's had prostatectomy followed by two rising PSAs above 0.2. If PSA doubling time is between three and nine months, those patients are potentially eligible for this trial. We are also looking for people who are not diabetic, but they should have a BMI of 25 or more because the mice models we tested were obese, and one of the side effects of metformin is weight loss. We did not want to give somebody who is skinny to start with a drug that makes them lose weight. Eligible participants should also not have their testosterone suppressed by hormonal therapy. We don't allow prior hormonal therapy, unless it was given during the primary treatment as an adjuvant or neoadjuvant therapy.

Those are the main inclusion criteria: BMI more than 25, no history of diabetes (hemoglobin A1C should be less than 6.5), testosterone more than 150, no prior hormonal therapy, and PSA doubling time is three to nine months. Then we'll do a CAT scan and bone scan to confirm they don't have metastatic disease.

Once we determine they are eligible, we randomize them to one of the two groups. One group (control arm) will receive observation for two months, followed by Casodex (bicalutamide) alone for 6 more months. The other group will receive metformin alone for two months, followed by a combination of metformin and Casodex (bicalutamide) for 6 months.

Because Casodex (bicalutamide) doesn't deprive testosterone, people have normal levels of testosterone, or sometimes higher levels. The total duration of treatment is 8 months or 32 weeks.

They come here to the NIH clinical center once a month, where we do blood work, a doctor evaluation, and we provide medication. During the trial, in addition to regular blood work, we research blood at the start, at the beginning of cycle three, and at the end of the trial. We're trying to understand the mechanism of how metformin works.

I know that you supply the medication, but are there any fees associated with participating in the trial?

Dr. Bilusic: No, there's really nothing else for the patient. Everything is provided, and all the care here at the NIH Clinical Center is free. Once a patient is enrolled on one of our protocols, we also support their trip to the NIH Clinical Center, so patients can come from all over the United States. We also provide a stipend for a hotel if they have to stay overnight. And we give them a meal voucher.

If someone reading this is interested, can he contact you directly, or is there somebody else?

Dr. Bilusic: They can contact me directly or Dr. Daniel Geynisman at the Fox Chase Cancer Center. Right now, we're enrolling at both Fox Chase and here at NCI. We hope that this combination will work for many patients, and that this study can help us understand how the combination works, and who it might work for in the future. Pp

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