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00:00.000 --> 00:13.600 Support for Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com.

00:14.100 --> 00:47.800 Welcome to Yale Cancer Answers with Dr. Anees Chaggar and Dr. Steven Gore. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about advances in the treatment of prostate cancer with Dr. Joseph Kim. Dr. Kim is Associate Professor of Internal Medicine in Medical Oncology at Yale School of Medicine. Dr. Gore is a Professor of Internal Medicine in Hematology and Director of Hematologic Malignancies at Yale Cancer Center.

00:48.200 --> 01:24.400 <vGore>As a cancer doctor, everybody's family has some friend who knows somebody, who knows somebody who has got prostate cancer and they want my opinion, which of course I am not a prostate cancer, so I try to help them as a lay person and a lot of this always focuses either around screening for prostate cancer or more often management of early stage prostate cancer whether it is surgery or radiation or whatever, but that is really not where you get involved with patients, is that right?

01:24.400 --> 01:25.400 <vKim>That is correct.

01:25.400 --> 01:33.200 <vGore>So you would be somebody that the patients would see if their prostate cancer is more advanced?

01:33.500 --> 01:55.600 <vKim>That is correct, but I do talk to our patients about PSA screening and I give lectures about this topic often, and many of these patients by the time they end up in my clinic they go through all of the PSA testing, definitive treatments, their cancer unfortunately comes back and having to see me to discuss further treatment options.

01:56.400 --> 01:59.800 <vGore>Got it, so you are the guy that none of us wants to see, right?

01:59.900 --> 02:03.700 <vKim>Correct in a way, but I love to take care of my patients.

02:04.200 --> 02:38.400 <vGore>And we are so glad that you are there to do so and do it so well. I think we obsess, men obsess, and I have had my family gone through this and obsessed about the best strategy that is going to minimize their chance of having a recurrence of cancer and maintain their ability to contain their urine and perform sexually if that is important to them, and now this indignity that somehow the cancer came back anyway, it has got to be devastating for patients.

02:39.100 --> 03:12.800 <vKim>Yeah, because many of the patients live with their disease for a long time and they go through a lot of ups and downs during

their disease. As you mentioned, many of the patients have complications from their prior therapy, some urinary incontinence at times, it could be sexual impotence and by the time they get to us, they develop spread of cancer that is causing some symptoms such as pains, weight loss, loss of appetite, and we try to find treatments for patients.

03:13.300 --> 03:28.300 <vGore>Now are these patients undergoing surveillance by their urologist or internist along the way of recurrence or it is just kind of wait and see and someday somebody comes in with bad back pain or something.

03:29.000 --> 04:17.800 <vKim>It sort of depends, for patients who underwent definitive treatments such as surgery or radiation treatment, usually a radiation oncologist or urologist for the most part should follow these patients after the surgery. They follow with a PSA, blood tests to detect the PSA level and they follow their symptoms, if they see a PSA rising, they prompt another discussion whether we need to draw another treatment versus can they simply watch and depending on how fast the PSA rises, often it initiates another treatment that can be in the form of hormone injections and also by the time they develop cancer spread on the scan, they also perform a discussion about how to treat those cancers.

04:18.500 --> 04:27.700 <vGore> I see, so sometimes you are treating people just because their blood level or PSA has risen and there is no evidence on the scanner or anything else of tumors anywhere?

04:28.200 --> 05:19.400 <vKim>That is correct. It does not always mean that we have to treat this actually. It depends on 2 settings, for patients who have done hormonal treatment before, just rising PSA after surgery or radiation treatment, you know if the PSA remains very low in level, then one could try a different radiation treatment, and continue to watch. If, however, PSA rises too quickly, too fast and higher levels, then sometimes this means initiating hormonal treatment. The other scenario is that the patients who have been on hormonal treatment and they still have rising PSA and have no disease on the CAT scan or the bone scan, then actually one of the latest risks which indicate that we could actually start hormonal pills to delay the time of developing metastatic disease.

05:20.100 --> 05:48.800 <vGore>How interesting. So when you say hormonal treatment, what exactly do you mean, I certainly know back in the old days and I am older than you, patients often were castrated surgically, more politely called orchiectomy, but basically is castration to get rid of their testosterone and they used to take a female hormone, Diethylstilbestrol, is that what we are talking about?

05:49.300 --> 06:23.800 <vKim>Before the invention of this hormonal injections, we used to perform orchiectomy, removal of the testicles, surgical castration, but you know now we have hormone injection that is designed to suppress the making of the testosterone from the testicles. We have a couple of what we call GnRH antagonists or agonists, these are often used by urologists and this

treatment alone can actually lower their PSA, can lower their testosterone and can lower the PSA and can control the disease for long periods of time.

06:24.400 --> 06:46.400 <vGore>I see. Now as a guy, I hear about lowering testosterone and we see a lot ads for people who want to build up their T, whatever right, what impact does this lowering of testosterone have on a variety things, I am particularly thinking of sexual function?

06:47.200 --> 07:01.100 <vKim>I understand, you know with hormone injections the first thing that patients experience is hot flashes, it is like male menopause, they will have flash symptoms, sometimes this can cause fatigue, there is sort of immediate symptom that one may experience with hormone injections.

07:01.900 --> 07:02.400 <vGore> Those get better?

07:05.200 --> 07:41.100 <vKim>They tend to get better overtime, but many of these patients get adjusted to this actually and this can be an ongoing side effect as long as they are on the hormonal treatment, and there are other long terms side effects of this treatment as well including effect on the bone health, cardiovascular health, endocrine functions get effected, also these treatments can cause what they call gynecomastia which is the enlargement of the breast tissue as well, so oftentimes they can cause pain, some irritation, some discomfort as well.

07:42.600 --> 07:50.100 <vGore>And what about sexual function, are people able to have erections and function sexually or is that sort of diminished or does libido go away?

07:50.800 --> 07:59.800 <vKim>With the hormone injection, the libido goes away, the psychological desire to have a sexual affair, it goes down, it goes away.

8:01.100 --> 08:03.500 <vGore>I imagine that is difficult for some of your patients and their partners?

08:04.600 --> 08:06.800 <vKim>That is correct. We counsel patients on that.

08:07.100 --> 08:31.500 <vGore>So I guess things are important if you are trying to live longer, but quality of life is also important, and it sounds like some of these situations may be a little elective or borderline if the only thing that is happening is the rising PSA right and there is not cancer and do I want to have the side effects, what is your advice for such patients?

08:32.500 -->09:34.600 <vKim>It sort of depends on the setting as I mentioned, you know in patients who have limited life expectancy with other medical problems, if the only issue is the rising PSA, I usually do not recommend initiating the hormonal treatments because although it is effective in achieving short-term goals, such as lowering the PSA, control the disease progression, it has now been showing to improve outcome in the survival, survival outcome exactly, so there are other factors to consider whenever we make these treatment decisions. For

patients who are young otherwise, no other medical issues, if their PSA is rising rapidly, we have to treat these patients very carefully because they are unfortunately destined to developing metastatic disease and sometimes giving them hormonal treatment can delay them to metastasis, can positively affect the outcome, overtime. So there are a lot of things to consider whenever we make these treatment decisions.

09:34.500 --> 09:38.200 <vGore> Right and you say sometimes the urologist makes that decision without your involvement, is that right?

09:39.100 --> 09:40.500 <vKim>Yeah, oftentimes.

09: 41.600 --> 10:02.200 <vGore>Do you have any therapies which can stimulate the libido and potentially have surgical help to have erections or really once you are on these therapies, you are just less sexual in that way.

10:03.400 --> 14:24.400 <vKim>I wish I could have a magic drug to stimulate the testosterone and give them their libido back, but what I often recommend to our patients is to stay physically active, exercise, a good balanced diet, stay active physically as much as they can and that is what I recommend.

10:25.800 --> 10:58.600 <vGore>Right, then I guess counseling can include helping people to appreciate other ways of physical expression of affection that does not necessarily require classical sexual activity involving the penis, I suppose, while challenging I guess. So then we have these patients where there actually is a recurrence either locally or distantly and I guess for prostate cancer, most things have changed since I was trained, the classic place for metastasis is in the bones, right?

10:59.500 --> 11:23.100 <vKim>That is correct. So for patients that have rising PSA, I always ask them whether they have a new bone pain because as you mentioned about 90% of our patients have cancer metastasis in the bones, so they will usually present with low back pain, worsening of the back pain, or any other bones that will prompt further evaluation.

11:24.800 --> 11:30.600 <vGore>Some of your patients are probably athletic and they may want to just say oh my arm is hurting because I worked out or my back, or something like that right?

11:30.900 --> 11:31.100 <vKim>Right, yeah.

11:32.100 --> 11:46.500 <vGore>How long in general in somebody who has a rising PSA, how much time can one expect from the hormonal therapies before the hormonal therapies do not work as well anymore?

11:47.600 --> 12:17.100 <vKim>The time it takes to develop metastatic disease simply by the rising PSA is usually about 5 to 7 years, actually there is a study that was done at Johns Hopkins, they followed these patients who had rising PSAs and they watched how long it took them to develop cancers on the scan and it takes about 5 to 7 years. The thing is we can as you mentioned we can

use hormonal treatment in between to delay the time or not, we can certainly talk about that.

12:18.500 --> 12:24.500 <vGore>So it is 5 to 7 years if you are not on hormonal treatment. Wow. So how much longer can you get if you are on the hormonal treatment?

12:25.600 --> 12:38.800 <vKim>So the studies have shown that by adding secondary hormonal treatment on top of hormonal injections, this can actually delay time of development of metastatic disease by about 2 years actually by adding a hormonal pill.

12:39.500 --> 12:54.500 <vGore>Wow and what is the hormonal pill as opposed to the, you said the injections are these things that turn off your pituitary gland and the pituitary gland no longer tells the testes to make testosterone right, so what does the pill do?

12:55.600 --> 13:29.800 <vKim>The pills actually work at the receptor level of the prostate cancer cells. These are what we call androgen receptor blockades. So if you think about the prostate cancer growth, there is always a signal coming in from the testosterone and the testosterone binding this androgen receptor in the prostate cancer cells and this androgen receptor, they go into the nucleus and grow and grow and forming a mass, this is how the cancer spreads. The thing is that these medications can block at the receptor level of the androgen receptor and thus, we can turn off the signal growth.

13:31.500 --> 12:54.500 <vGore>Fascinating. I am going to want to take this up in the second half, but right now we are going to take a short break for a medical minute. Please stay tuned to learn more about prostate cancer and early phase clinical trials with Dr. Joseph Kim.

Medical Minute: Support for Yale Cancer Answers comes from AstraZeneca, proud partner and personalized medicine developing tailored treatments for cancer patients. Learn more at astrazeneca-us.com.

13:59.400 --> 14:40.400 This is a medical minute about melanoma. While melanoma accounts for only about four percent of skin cancer cases, it causes the most skin cancer deaths. When detected early, however, melanoma is easily treated and highly curable. Clinical trials are currently underway to test innovative new treatments for melanoma. The goal of this specialized programs of research excellence in skin cancer or SPORE is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improved diagnosis and treatment. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

14:11.300 --> 15:07.800 <vGore> Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, I am joined tonight by my guest, Dr. Joseph Kim and we have been discussing prostate cancer. Joe, before the break, you were telling me about these additional pills which I understand block the affect of testosterone

on the cells at the cellular level. Why not use that in the front rather than turning off the testosterone altogether?

15:08.800 --> 15:48.600 <vKim>That is a very good question. There is actually a lot of research going on to answer that question. So what we know is that in recent years, we used these agents in later stage, but now actually we are using these agents in early, newly diagnosed metastatic prostate cancer. So before, we used to give them hormone injections for patients with newly diagnosed metastatic prostate cancer, but now we are actually adding things such as hormone pills that I talked to you about which can be in the form of chemotherapy or radiation therapy, but we do use hormonal pills in early setting, but not in localized setting.

15:49.800 --> 15:55.500 <vGore>I see and do the hormone pills have fewer or different side effects from the injections?

15:56.400 --> 16:05.500 <vKim>I would say if we add it to hormone injection actually it has a little more hot flashes, sometimes this can raise the blood pressure, it does come with a bag of side effects unfortunately.

16:07.800 --> 16:08.100 <vGore>You would never use the pills by themselves?

16:08.900 --> 16:09.500 <vKim>Correct, not by themselves.

16:10.800 --> 16:12.500 <vGore>Was that ever studied or nobody wants to take that risk?

16:13.800 --> 16:23.500 <vKim>I do not think it has been studied as a single agent because the hormone injection has been launched for long period of time and that has been the backbone of the treatment and it is very effective for prostate cancer.

16:24.800 --> 16:28.500 <vGore> And it does not sound like the side effects of the pills would necessarily be better.

16:29.800 --> 16:30.100 <vKim>Correct.

16:31.800 --> 16:36.500 <vGore>That is too bad, okay. So now you have got your patient who has been on may be double hormonal therapy, is that right?

16:37.500 --> 16:38.300 <vKim>That is correct.

16:39.100 --> 17:07.500 <vGore> And unfortunately their cancer might be getting worse, either it is newly metastatic it sounds like or the metastasis have gotten worse. You know, when I was training, it was thought if the chemotherapy did not work for prostate cancer and once the hormonal therapy failed, then you are talking about supportive care, palliative care, treating symptoms of stuff, that is not the case any more, right?

17:08.300 --> 17:47.100 <vKim>It is not the case anymore, really in recent years, we have about 5 or 6 new agents approved this past decade actually in treatment of metastatic hormone resistant prostate cancer, and we have new chemotherapy,

I know the chemotherapy about 15 years ago was the only chemotherapy that was available in treating metastatic prostate cancer, but we have different forms of chemotherapy, different hormonal oral agents, and also other intravenous radiation treatment to treat patients with cancers in the bone.

17:48.800 --> 17:49.500 <vGore>How do you give radiation intravenously?

17:50.800 --> 18:36.500 <vKim>That is basically what we call a radionucleotide that is because the bone metastases are very common in patients with prostate cancer and they have a lot of complications from the bone metastasis needing radiation treatment, cold compression, fractures, a lot of complications, right, so these medications are given intravenously, it is usually done by nuclear medicine physicians and these medications target cancer growing in the bone. Whenever there is a bone turnover, these medications will go to this area and deliver their high energy radiation and this medication is shown to improve survival, palliative symptoms, so in a way it is a very effective treatment we have.

18:39.600 --> 18:41.500 <vGore>And does that radiation affect normal tissue as well?

18:42.900 --> 18:49.400 <vKim>Actually this is designed to target the bone only, so it does not go to other visceral organs, it does not go to other tissues.

18:50.500 --> 18:51.200 <vGore>So the side effects are few?

18:52.100 --> 18:53.100 <vKim>Yeah, they are very minimal.

18:54.800 --> 19:03.500 <vGore> Wow, that is so exciting, I did not know about that. Okay, that is certainly cool and what are some of the other treatments or kind of treatments that have more recently been approved?

19:03.600 --> 19:40.500 <vKim> In terms of approval, there are different generations of this androgen receptor antagonist, the new agent, the hormone pills, and they tend to have better side effect profiles than the prior ones and large trials have been shown to improve survival, so there are different generations of hormonal pills. There are other agents in development in prostate cancer, they are not approved therapy, I am not sure if I can talk about investigational agents or not, but there is clearly a lot of research going on to study new agents to treat prostate cancer.

19:41.800 --> 19:50.500 <vGore>Unless you are under confidentiality appointments from any particular study you are doing, we are certainly able to talk about research you are doing if there is something interesting.

19:51.800 --> 20:25.500 <vKim>So I think in recent years, what we know about prostate cancer is that not all prostate cancers are little but clearly there are some patients who have very little phenotype of the prostate cancer. So what investigators did is that they looked at whole genome sequencing of metastatic prostate cancer, the DNA basic and they identified that about 20% of the patients with metastatic prostate cancer harbored mutations in genes called BRCA, ATN, those are the genes that are involved in DNA mechanism.

20:26.800 --> 20:36.900 <vGore>Okay, hold on, you have thrown a lot of letters at me. So, you have thrown out some letters that refer to particular genes right and these genes are mutated in these patients?

20:37.400 --> 20:39.900 <vKim>They are mutated in these patients.

20:40.800 --> 20:43.100 <vGore>And these are genes that make proteins that would usually help fix DNA if it is broken, right?

20:43.300 --> 20:44.500 <vKim>That is correct.

20:45.100 --> 20:46.100 <vGore>Did I get that right?

20:46.800 --> 20:47.100 <vKim>Right.

20:47.800 --> 21:02.400 <vGore>Okay. So now we are learning if I understand you correctly that about 20% of prostate cancer patients, the prostate cancer has mutation in one or more of these genes that means that they cannot repair their DNA so well. Is that right?

21:03.100 --> 20:03.300 <vKim>Right.

21:03.800 --> 21:04.900 <vGore>Okay, why do I care about that?

21:05.800 --> 21:37.100 <vKim>So what we do for these groups of patients is these patients tend to respond quite well to a new drug called a PARP inhibitor and actually there are some approved PARP inhibitors in treatment of other malignancies, such as breast cancer or ovarian cancer. What we are learning is that about 20% of our patients with the prostate cancers may derive benefit from this class of medications. So there are several clinical trials to look into this question.

21:38.600 --> 21:46.800 <vGore>Do they receive these PARP inhibitors as a single agent or are you giving them with other drugs?

21:47.600 --> 22:01.200 <vKim>We give them with other drugs, with hormone injections, because hormone injections do not go away, patients with metastatic prostate cancer, they remain on hormone injections for the rest of their life and we are adding this PARP inhibitor on top of the hormone injection.

22:01.800 --> 22:29.300 <vGore>I see. So these PARP inhibitors further inhibit the DNA repair, right. So then if the DNA is all messed up, then the cell will die I guess, but in some cases as I recall for some cancers, you use the PARP inhibitor in association with something that will damage the DNA and make the damage worse. Is this the case in what you are telling me?

22:30.400 --> 22:51.400 <vKim>I think we can add another medication to further damage the DNA to be more effective, but to start off we need to understand what the side effect profile is of this agent by itself and we would better understand the efficacy of this agent. Clearly, there are several trials combining PARP inhibitors with other agents.

22:53.700 --> 23:04.900 <vGore>I see, gotcha and so are these trials limited to gentlemen whose cancer is shown to be deficient in one of these DNA repair enzymes or mutated in one of these DNA repair enzymes?

23:05.700 --> 23:18.100 <vKim>So it depends on the design of trial and the question we are asking in the trial. Clearly there are trials that are ongoing that are selecting patients with this mutation. If you have a mutation, you can participate, but if you do not, unfortunately you cannot participate.

23:19.600 --> 23:22.900 <vGore>It does not sound like you would be missing out because it is probably not appropriate.

23:23.600 --> 23:38.800 <vKim>Correct, exactly, that is not a good match, that is how I frame it, but for patients if they have mutations, one can give this medication in combination with another medication to see if they can overcome this limitation.

23:39.600 --> 24:11.400 <vGore>I see, gotcha. Now I know when you were recruited to Yale which was a little bit before I was, you came from the National Cancer Institute if I recall and you were very interested in what we call early phase drug development and you wear to hats here right, you participate with urologic oncology and you're part of the group that is really developing very, very early phase clinical trials, can you tell us what that is like to some of these drugs have never been put in a human.

24:13.100 --> 25:16.600 <vKim>Right, so the clinical trial as you know is the main engine of oncology, what I mean by that is that it is the only way we can advance the field by bringing novel therapy to our patients who otherwise have no other good treatment options and this is the only way you can advance to finding better treatments. Our patients tend to be sicker and there are unfortunate cases because they are going through different standard therapies and they have no other options left and we go to them and we talk about these novel therapies. Novel means, new, it does not always mean effective, does not always mean that this is it for the patient, right. So we have to have a very good balanced discussion with our patients, and whenever I talk about trials, I talk to them about their alternative options if any and we talk about the study design and the clinical trials. It does bring a lot of unique challenges for patients and in the field.

25:15.500 --> 25:50.400 <vGore>I have read studies where patients who participate in these early phase trials and the doctor told them they were really just trying to study the side effects and it is unlikely that this will actually help your cancer and then when they interview the patient, the patient states you know what do you think we might get out of this, they say, I may live longer and I might be cured. It is not clear whether that is what patients want to believe or need to believe or whether that is what they understood from what the doctor was saying. What is your experience with that?

25:50.900 --> 25:56.700 <vKim>So I think we have to be smart about how to

find those trials for patients, that is what we want to do.

25:57.100 --> 25:57.800 <vGore>We want to give them hope.

25:57.100 --> 26:17.700 <vKim>I think we want to have a better understanding of the patients genetic profile to see if a certain drug can be a better option for this patient, I think we need to have a better understanding about the patients disease status, actually.

26:18.300 --> 26:22.100 <vGore>So how do you identify a drug that may be particularly interesting, like you started setting this PARP inhibitor?

26:23.400 --> 26:53.200 <vKim>So as I mentioned we do actually work with tumor profiling for patients. You know what it is. This is a form of biopsy sample of the tumor, we actually sequence the DNA and we sort of identify what kind of mutation this tumor has. If the patient's tumor has a specific mutation, then we think that drug X may be effective, then we offer the trial with that medication. So we try the drug that matches patients with the trial.

26:54.300 --> 26:59.800 <vGore>Is every mutation that you find a critical mutation for the cancer, that if you block it, the cell will die?

27:01.900 --> 27:12.300 <vKim>It is hard to say. We try to make predictions depending on the prevalence and what the biologies of the mutation are, but it is not always the case unfortunately.

27:14.300 --> 27:25.800 <vGore>Alright and I have to imagine that for certain mutations that are particularly rare, as a scientist at Yale for example, you might see 1 in 5 and you cannot really do a study about that.

27:26.100 --> 27:40.800 <vKim>That is correct. So it does require a lot of collaboration and we do trials with other institutions all throughout the country to find these rare mutations and are still be able to give them a treatment that may be more effective.

27:41.600 --> 28:01.800 <vGore>Right, so you have to start to develop your own career and play in the sandbox very well with everybody else. It is kind of like a village trying to help this field. What do you think is the most exciting thing coming down the pipe for these patient whose cancer has failed to stay in check after all this time and all these treatments. Anything really exciting?

28:02.600 --> 26:59.800 <vKim>I think for prostate cancer, as I mentioned, there is a lot of research going on using this PARP inhibitor and there are a couple of agents that have earned actually what they call breakthrough therapy designation for prostate cancer and we have several trials using those agents in combination with other conventional therapies. So those are quite promising, again we are looking for the patient with the mutation and we also have trials for patients without those mutations. So I think we are trying to expand the benefit of these agents for the greater population.

Dr. Joseph Kim is associate Professor of Internal Medicine in Medical Oncology at Yale School of Medicine. If you have questions, the address is cancer-answers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.