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GENITOURINARY CANCERS · 09.20

PARP Inhibitors Will Add a Treatment Option for Men with Metastatic Prostate Cancer

THE MAINSTAY OF TREATMENT for metastatic prostate cancer has long involved suppression of the hormones that fuel the disease, and that strategy can spark a remission that lasts many years.

But in some cases, disease becomes resistant to these drugs and needs different modes of treatment. The good news is that the Food and Drug Administration recently approved two drugs that are new to prostate cancer treatment and could help nearly one-third of men with metastatic disease.

In May, both Lynparza (olaparib) and Rubraca (rucaparib), known as poly-ADP ribose polymerase (PARP) inhibitors, were approved to treat men with DNA repair problems that either developed in their tumors or were inherited in their genetic codes. At that time, we explained how these drugs kill cancer cells by augmenting their existing DNA repair glitches, making it more difficult for the cells to fix themselves when damaged (curetoday.com/link/280). PARP is a protein involved in DNA repair, and these drugs work by inhibiting its activity.

In this special issue of *CURE®*, we bring you a more in-depth look at the advent of PARP inhibitors in the treatment of prostate cancer and what it will mean to patients. We discuss who may benefit and how these patients can be identified, what kind of responses and side effects can be anticipated and what questions patients should ask to ensure they will be offered these drugs if they are good candidates for the treatments.

Elsewhere in the magazine, we offer another feature on a recent drug approval in metastatic disease — in this case, urothelial cancer. While multiple immunotherapies known as checkpoint inhibitors have been approved to treat this type of bladder cancer since 2014, the recent approval of one such drug, Bavencio (avelumab), to be given just after initial treatment with platinum chemotherapy, is the first to be used in this earlier setting and spark an improvement in overall survival. In our article, we look at the survival benefits that are possible with this drug and the complex issue of how to determine who is most likely to benefit from it.

A third feature is devoted to an issue that is vitally important to survivors of prostate and bladder cancers: the sexual side effects that can arise from treatment. The article explores the best ways to manage these side effects when they cannot be avoided or reversed.

In a look at a rare cancer whose patients are affected by a lack of public awareness and research, we offer a section on penile cancer, including an interview with a caregiver and a conversation with an expert on clinical trials. Attention also is given to the ramifications of the COVID-19 pandemic in an article that suggests long-term adoption of some of the changes to kidney cancer care that have arisen from the crisis.

We hope these updates will leave you feeling better informed about therapies, research and side-effect management, helping you to make good decisions about your care both during and after treatment. As always, thank you for reading.

MIKE HENNESSY SR.
Chairman and Founder

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Detecting Prostate Cancer Without Overtreatment Is Difficult

A DIFFICULT LINE TO WALK in some cancer types is that between widespread screening to detect early disease and lower the death rate versus the overtreatment and associated consequences that can arise from it. This is particularly true when it comes to prostate cancer.

There has been a lot of debate about screening in asymptomatic men to check blood levels of prostate-specific antigen (PSA), a protein that tends to rise when prostate cancer is present. It's an imperfect test, since rising levels of PSA can indicate issues other than cancer, but it's the best way to screen that's available now.

PSA screening was once widely administered as part of routine wellness visits, but that changed in 2008 after the U.S. Preventive Services Task Force (USPSTF) advised against it in men 75 and older, and again in 2012 when the task force recommended against its routine use in all men. In 2018, the task force relaxed its rules, suggesting that men 55 to 69 make individual decisions about whether to screen but that men 70 and over should not take the test.

According to a study discussed in this issue of *CURE®*, the rate of advanced prostate cancer in men 50 or older demonstrated an upward swing between 2005 and 2016, while the frequency of early stage prostate cancers dropped. The study's authors believe those changes may be a direct result of the USPSTF's recommendations, which were based on concerns about overtreatment — biopsies and therapy that can cause side effects and lower the quality of life in men whose disease, if undetected, would never have harmed them.

At the time the USPSTF made its recommendations, one large clinical trial had demonstrated a benefit associated with PSA screening, but two others had not. However, it was discovered later that one of the trials that showed no benefit, due to faulty data analysis, had underestimated the testing's value. According to a recent analysis, that trial and the one that originally showed a benefit now agree that there was a 25% to 30% relative reduction in the risk of prostate cancer death in men who had screening compared with no screening.

Yet, based on the USPSTF's recommendations, a smaller number of men were screened. That surely saved some patients from overtreatment, but at the same time it seems to have driven up the rate of advanced prostate cancers. Another problem with skipping screening is that it can deny men with low-grade prostate cancers the option of undergoing active surveillance so they will know if their disease starts growing quickly and needs more aggressive therapy.

"Based on the USPSTF's recommendations, a smaller number of men were screened. That surely saved some patients from overtreatment, but at the same time it seems to have driven up the rate of advanced prostate cancers."

So far, we have not seen a rise in death rates from prostate cancer; in fact, there was a marked decline between 1993 and 2017, but it may be too soon to see an effect from the decline in screening. In any case, it's crucial to the well-being of patients that we move the diagnostic trend toward finding disease before it has reached advanced stages.

In our article, researchers discuss ways to strike a balance between the harms and benefits of PSA screening by customizing the process, including spacing out the tests and screening only those under age 70. Other advancements could include refining active surveillance for men who have elevated PSA and lower-grade disease and creating new diagnostics, such as DNA-based technologies and systems that measure how quickly PSA levels rise over time. Needed just as much are strategies that will help patients and their doctors choose the most appropriate treatments or monitoring techniques.

All of these developments will help ensure that patients receiving local therapies such as radiation or surgery will have the best chance at longevity without experiencing life-changing side effects from either their disease or therapy — and that those who don't need treatment can avoid it. Researchers and clinicians are working on the different parts of this puzzle, and early diagnostic technologies are advancing quickly, yet it is difficult to say when the next version of prostate cancer screening guidelines will be able to reflect this progress and bring the PSA screening debate to a close.

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MIKE KITADA

Finding a Balance in Screening

After a recommendation against routine prostate cancer screening, rates of early disease declined while the incidence of advanced disease rose. The trend highlights the difficult balance between screening and potential overtreatment. By BETH FAND INCOLLINGO

THE RATE OF ADVANCED prostate cancer in men aged 50 or older continued to rise between 2005 and 2016, even as the frequency of early stage prostate cancers dropped, according to a study published in the *Journal of the National Cancer Institute*.

The study's authors suggest that the redistribution of diagnoses may be associated with recommendations against routine screening for the disease made by the U.S. Preventive Services Task Force (USPSTF) in 2008 and 2012.

In fact, previous studies found that the U.S. incidence of local-stage prostate cancer dropped while the incidence of regional- and distant-stage disease increased soon after the USPSTF made its recommendations against routine screening, Dr. Ahmedin Jemal and fellow researchers at the American Cancer Society (ACS) noted. Their study looked at whether these patterns persisted in the longer term, through 2016.

In 2008, the USPSTF recommended against prostate-specific antigen (PSA) testing in men aged 75 and older, and in 2012, the panel of experts recommended against the screening in all men. In 2018, the USPTF recommended individual decision-making about screening for men aged 55 to 69 and said that men 70 and older should not be screened.

PSA is a protein produced by cells in the prostate gland, but if the level of the protein reaches abnormally high levels in the blood, it could signal that prostate cancer is present. PSA testing is controversial because it is not a guaranteed way to detect prostate cancer. Levels of the protein can rise for reasons other than prostate cancer, leading to unnecessary biopsies that can cause pain, bleeding or infection and raise anxiety for patients. And while a re-analysis of two large clinical trials showed a 25% to 30% relative reduction in the risk of prostate cancer death with screening versus no screening, the testing can lead to the identification and treatment of slow-growing prostate cancers that, if never found, would not be harmful. In fact, in those two trials and one other, 16.4% to 50.4% of prostate cancers were overdiagnosed, the USPSTF noted in its 2018 recommendation. This is problematic, the organization noted, because treatment for prostate cancer can leave patients with long-term side effects, including incontinence and erectile dysfunction.

The USPSTF's recommendations have been controversial, with some experts believing the guidelines have led to a larger proportion of prostate cancers being diagnosed at later stages, when they pose a greater threat to patients' lives and may require more aggressive treatment.

According to the ACS, the rate of routine PSA testing has dropped since the USPSTF recommended against it. A national survey of men aged 50 and older showed that their past-year routine PSA testing rates declined from 40.6% in 2008 to 38.3% in 2010 and 31.5% in 2013, remaining unchanged in 2015, an ACS press release stated.

STUDY RESULTS

In the recent study, the team led by Jemal, a cancer epidemiologist who heads the Surveillance and Health Services Research Program at the ACS and is an adjunct professor at Emory University in Atlanta, used data from the U.S. Cancer Statistics Public Use Research Databases to analyze how much the rate of invasive prostate cancer changed each year from 2005 to 2016 in men aged 50 and older. Within the study, the men were divided into groups based on disease stage (local, regional or distant), age (50 to 74 versus 75 or older) and race/ethnicity (all races and ethnicities, non-Hispanic Whites and non-Hispanic Blacks).

The researchers found that, across patients of all participating races and ethnicities, the incidence of local disease dropped by 6.4% per year from 2007 to 2016 in men aged 50 to 74. In men aged 75 and older, the incidence of local disease declined by 10.7% annually from 2007 to 2013 and then stabilized from 2013 through 2016.

In contrast, the incidence for prostate cancer that had spread to distant parts of the body rose in both age groups during the study period. For example, distant-stage incidence in men aged 75 and older increased by 5.2% per year from 2010 to 2016. »

"These data illustrate the trade-off between higher screening rates and more early stage disease diagnoses (possibly overdiagnosis and overtreatment) and lower screening rates and more late-stage (possibly fatal) disease," the authors wrote. "Several modeling studies, however, showed that the harms associated with higher PSA screening rates can be mitigated while preserving the benefit of screening."

That could be done by waiting longer between screenings, raising the PSA level associated with the need for biopsy in older men and restricting routine testing to men younger than age 70, the authors suggested.

Additionally, the study identified a substantial decline in racial disparity in the incidence of distant-stage disease, largely confined to men aged 50 to 74 years, which coincided with a steeper increase in distant-stage incidence in non-Hispanic White men. Nevertheless, incidence rates in non-Hispanic Black men remained two to three times as high as in non-Hispanic White men.

"Reasons for this disparity are not fully understood, but in part are thought to reflect differences in lifestyle factors, biological susceptibility and access to care," the authors wrote. "Obesity and cigarette smoking are more prevalent in (non-Hispanic Black) than (non-Hispanic White) men. Furthermore, the association of obesity with prostate cancer risk is stronger in (non-Hispanic Black) men."

Across the whole study population, the researchers suggested that family history and cigarette smoking were unlikely to be responsible for the changes in prostate cancer incidence. However, they said that the importance of an increase in excess body weight since the 1970s deserves study.

Their analysis did not cover the period after 2018, when USPSTF recommendations changed again; the impact of that change on prostate cancer rates has not yet been measured, according to the ACS.

"Regional- and distant-stage prostate cancer incidence continue to increase in the U.S. in men aged 50 years or older, and future studies are needed to identify reasons for the rising trends," the authors concluded.

Jemal said that all men aged 50 and older with a life expectancy of at least 10 years should receive information about the potential benefits, risks and uncertainties of prostate cancer screening in order to make informed decisions with their health care providers about whether to undergo testing.

Hannah Slater *contributed to this story.*

It's Rare, But Be Aware

A woman shares her late husband's journey with advanced penile cancer to help others receive a diagnosis early, when the disease is still highly treatable and even curable. By BETH FAND INCOLLINGO

CHRIS EHRING DIED 11 WEEKS after learning he had penile cancer. He had been receiving treatment for only five weeks.

His wife, Kinnet Ehring, is left to face the emotional aftermath, and she has responded by reaching out to others to raise awareness about the condition.

Diagnosed in just over 2,000 men in the United States each year, penile cancer is curable in early stages with appropriate treatment, but it's exceedingly rare, which is why men often don't recognize it or seek immediate medical care. Many also don't know that it almost exclusively affects uncircumcised men or that a major risk factor is HPV infection, which can sometimes be prevented with a vaccine. Other known risk factors include chronic inflammation, obesity, HIV/AIDS, tobacco use, UV light treatment for psoriasis and age.

Aside from his age, 73, Chris didn't have any of those risk factors.

Initially, multiple physicians treated Chris with antibiotics for what they assumed to be an infection, and Kinnet remains upset about how long it took for him to receive an accurate diagnosis: stage 4 penile cancer that had spread to the inguinal lymph nodes in his groin and to his thorax. She also believes that treatment should have been started sooner once the condition was determined to be advanced, late-stage cancer.

Kinnet, of West Barnstable, Massachusetts, sat down with *CURE*® to discuss her late husband's experience with penile cancer and the need for greater awareness about the disease. Her goal: for other men to learn from Chris' experience so they can receive prompt diagnosis and treatment.

CHRIS and **KINNET EHRING** enjoy an outing together for a meal.

PHOTO PROVIDED BY KINNET EHRING

Q ***CURE*®: What led up to your husband receiving his diagnosis?**

A **Kinnet Ehring:** Chris had had a lot of pain and a burning sensation in his penis, starting around late December or early January. On Jan. 17, he went to see his primary care physician, and I have some issues with this particular doctor. He did not even examine Chris' penis. He said he thought it sounded like a urinary tract infection and put him on antibiotics.

Four days later, the doctor called Chris to say, "Good news. It's not a urinary tract infection." Chris said, "That's not good news. Good news would be that it was a urinary tract infection and that this antibiotic would clear it up. Because if it's not a UTI, then what the heck is it?"

The primary care physician suggested that he call a urologist, but he couldn't get an appointment until three weeks later. The doctor didn't call the urologist himself and make an emergency appointment — even though Chris had a history of bladder cancer back in 2004, which he beat. I think every medical care professional should always think to him or herself: "This could be cancer." That should be the default position.

Part of the problem is that penile cancer is an orphan malignancy because it affects fewer than 200,000 people in the United States, so many people have never even heard of it.

Chris saw the urologist for the first time on Feb. 12, and by then his penis had gotten more ulcerated. And so what did the urologist do? Put him on a higher and stronger dose of antibiotics and told him to come back the following Tuesday. When there was no improvement, he admitted Chris to St. Elizabeth's Medical Center in Boston.

Over the next couple of days, their focus remained on some type of infection. Finally, on Friday, Feb. 21, they did a biopsy on him, and it came back positive for squamous cell carcinoma in both his penis and his lymph nodes. A CT scan showed that the cancer had also spread to his chest. He was discharged on Feb. 27 with a plan to go back on March 10 for a PET (positron emission tomography) scan and to meet with a medical oncologist from Dana-Farber Cancer Institute through St. Elizabeth's satellite location. »

Q What was the course of his treatment?

A The PET scan pretty much confirmed what the CT scan had shown a couple of weeks prior to that.

During the appointments with the medical oncologist and urologist, they said basically the same thing they said before he was discharged from the hospital. The plan was that he was going to start treatment there on March 25, so now we had to wait again. And I was getting really anxious because nothing was being done and the cancer could have been growing.

Because the disease was so advanced, potentially curative surgery to remove part or all of the penis was not an option. Chris' treatment with radiation five days a week and chemotherapy weekly started on March 25 at Cape Cod Healthcare's Davenport Mugar Cancer Center and was supposed to end around May 7. Then he was going to take a two-week break before he started his second round of a double dose of chemo with no radiation treatment. We never got to that point. As a matter of fact, he died the day after he was supposed to have received his last radiation treatment.

Q You've said that you don't feel your husband's care team gave him the information he needed to choose the best treatment plan. What went wrong?

A There was never really any discussion of Chris' prognosis or objectives. I think, had he known he was going to die so quickly, that he might not have opted for the radiation treatment because it was so incredibly excruciating for him.

Every time I drove him to treatment, which was every morning, I had to make sure I avoided every crack in the road. The railroad tracks were a big challenge. I used to take them very, very slowly, and one time a guy behind me in a pickup truck honked his horn and passed me and flipped me the bird because I was taking too long to go over the railroad tracks. But I had to do that because Chris was in so much pain. It was just a horrible experience for him. I feel so bad that he had to go through that only to be gone.

I'm still at a loss as to why he went so quickly. I've asked his oncologist to set up an appointment to meet with me to give me a postmortem as to what happened and why he died so quickly.

Q What is your advice to others who might have unexplained penile symptoms?

A If there's anything you see on your penis that looks as if its characteristics have changed, such as swelling, changes in color or lesions, go see a doctor, preferably a urologist, immediately. And if the doctor's opinion is that it's a UTI, insist that he examine it even if he doesn't want to. If he doesn't want to, then he's in the wrong line of work.

And just be aggressive about self-care. Women give themselves monthly breast examinations; maybe men should do the same with their penises. I've done a lot of reading on this, and I learned that a lot of men have unnecessarily died from penile cancer because they were too embarrassed to show their penis to a doctor. And that's just silly.

> **"I learned that a lot of men have unnecessarily died from penile cancer because they were too embarrassed to show their penis to a doctor. And that's just silly."**
>
> *—KINNET EHRING, patient advocate*

Again, I also think that every doctor should take this default position with patients who come in complaining of pain: They should all say to themselves, "This could be cancer. Other things cause pain too, but let's rule out the cancer first."

Q Besides speaking with *CURE*®, what are you doing to help raise awareness about penile cancer?

A If you ask the average person if they've ever heard of penile cancer, they'll say, "No, I never even knew you could get cancer there."

Even some doctors may not know about this condition, so this should be part of continuing medical education.

Because the disease doesn't get enough attention, I started a giving page, and we've raised over $5,300 for the Dana-Farber Cancer Institute. My goal is to get to $10,000, and I hope I reach that goal within the year.

I've also talked to Dana-Farber's philanthropic division about organizing an event to raise money and awareness, like maybe a regatta, because my husband was a big racing sailor who was very active in all sorts of regattas throughout his life.

The proceeds will go to Dr. Guru P. Sonpavde, a genitourinary oncologist who directs the bladder cancer program at Dana-Farber, and whom really Chris liked during the one telehealth visit they had. The funds will be used for a two-prong purpose: One is to raise awareness among doctors that penile cancer exists. The other is to investigate the best ways to treat it.

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Donations can be made by visiting
http://danafarber.jimmyfund.org/goto/chrisehring.

Trial Studying Rare Cancer Offers Hope

New treatments are needed for penile cancer, but it's difficult to test drugs in clinical trials because the disease is so uncommon.

By BETH FAND INCOLLINGO

DR. GURU P. SONPAVDE

PATIENTS WITH METASTATIC penile cancer face a poor prognosis and would benefit greatly from therapies more effective than chemotherapy. Yet, scientists face challenges in making that happen, and as a result not much progress has been made in recent years.

"Research in penile cancer is severely, severely lacking," says Dr. Guru P. Sonpavde, an oncologist with Dana-Farber Cancer Institute in Boston. "We don't understand its tumor biology, and there are not a lot of people doing basic or translational research in penile cancer." In fact, he says, there are only about a dozen clinical trials across the globe testing treatments for the rare cancer.

Fortunately, Sonpavde said, one of those trials is large and promising, and there is reason to believe that more trials will include patients with penile cancer in the future.

The first phase 3, randomized trial ever to test therapies for the condition, the global International Penile Advanced Cancer Trial (InPACT), includes patients with locally advanced disease divided into three groups. Men in all of the groups will undergo surgery to remove part or all of the penis and any affected lymph nodes; in addition, the patients in one group will receive chemotherapy before surgery while those in another group will receive presurgical chemoradiotherapy. The goal is to enroll 400 patients — about 12 times as many as are included in typical trials of drugs for this population, Sonpavde says.

The trial is recruiting patients, and those interested can learn more at **clinicaltrials.gov/ct2/show/NCT02305654**. Patients also can ask about participation by contacting the study's chair, Dr. Curtis A. Pettaway of The University of Texas MD Anderson Cancer Center in Houston, at 713-792-3250 or **cpettawa@mdanderson.org**.

"It's tough, logistically, to open a trial globally for a rare cancer, because what it means is you really have to open it in a lot of sites, a lot of institutions, to capture all these patients," Sonpavde says. "So, that obviously raises the issue of costs. Can you really open a trial in a thousand institutions that will only enroll a small number of patients?"

Sonpavde has faced this dilemma himself. He was an investigator on two trials for penile cancer treatments, both of which closed due to low enrollment.

One trial tested a drug that inhibited the HER2 protein, which can sometimes be overexpressed in penile cancer, fueling the disease. "We opened the trial in five institutions, but we had huge challenges in accruing patients," Sonpavde recalls. "We got the word out, but these patients are scattered all over, and sometimes it's tough to get patients to travel to a handful of sites scattered over the country. These patients have advanced metastatic disease, and may have really poor (health). And frequently, a lot of them have lower socioeconomic status, so it's very hard for them to travel to a major academic center 300 miles away. We had a second trial that was looking at the exciting immunotherapy drug Keytruda (pembrolizumab), but even that had trouble accruing."

Another barrier to trials, Sonpavde said, is that industry will remain uninspired to develop a drug specifically for penile cancer as long as information is lacking about the key genetic alterations that drive it. However, he said, pharmaceutical companies may develop drugs for other cancers and then, if testing proves effectiveness, expand the uses of the medications to include the treatment of penile cancer.

Besides a large international effort such as the InPACT trial, a way to include patients with penile cancer in research would be to enroll them in "basket trials," in which patients are treated based on a genetic mutation in their tumor, rather on where the cancer developed in their body, Sonpavde said.

Drugs of interest could include HER2 inhibitors or Erbitux (cetuximab), which targets the protein EGFR, which also has shown some early activity in patients with penile cancer. In addition, immunotherapies such as Bavencio (avelumab) are being investigated.

Patients and their doctors should not overlook the fact that one immunotherapy already is approved for use in penile cancer, as long as a patient's tumor has the appropriate characteristics, Sonpavde pointed out. Keytruda is approved across all cancer types in cases where a patient's tumor expresses a large number of genetic mutations (a condition known as tumor mutational burden-high) and has progressed after treatment with a previous therapy, Sonpavde said. He added that Keytruda is approved to treat any tumors that have mismatch repair deficiencies or are microsatellite instability-high, meaning that they have trouble repairing their own DNA. It also is possible that specific mutations could open the door to a clinical trial.

"I would encourage genomic profiling of patients' tumors just to look for (those alterations)," Sonpavde said.

DANA-FARBER CANCER INSTITUTE

CHRISTOPHER SCHADE, a bladder cancer survivor, worked hard to recover from his cancer treatments and heart surgery so that he could get back on his bike and feel the wind in his face.

PHOTO PROVIDED BY CHRISTOPHER SCHADE

Maintaining an Advantage

Patients with advanced or metastatic bladder cancer, after responding to initial treatment with chemotherapy, may preserve their health improvements by starting immunotherapy immediately.

By DEBORAH ABRAMS KAPLAN

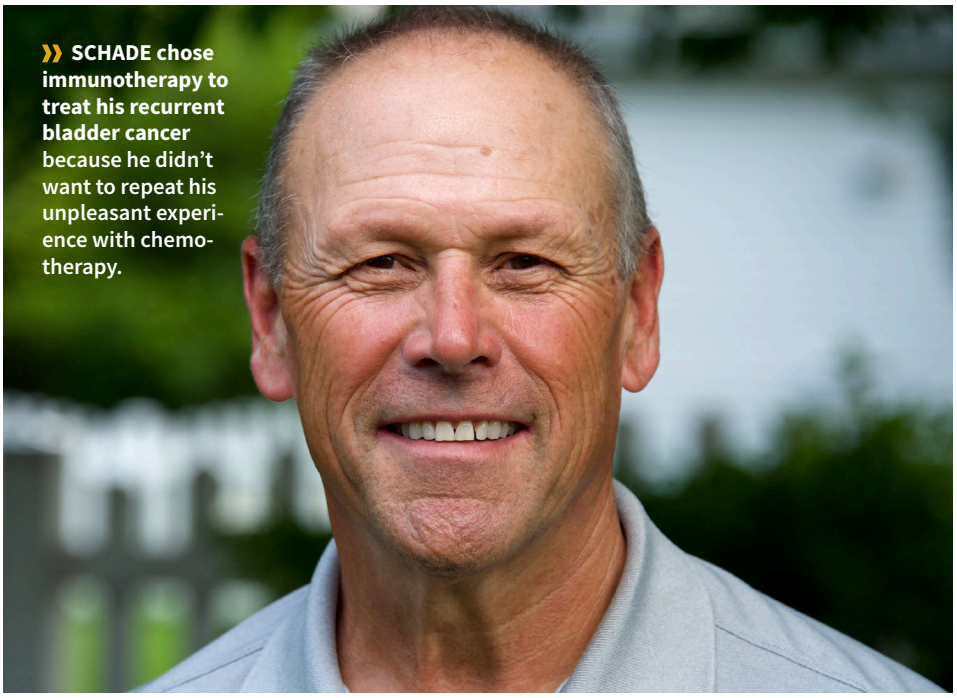
When Christopher Schade noticed blood in his urine in 2010, he found himself at the beginning of a long and challenging road.

A urologist found a tumor in his bladder, and Schade, now 66, received a diagnosis of urothelial cancer, the most common form of bladder cancer. The doctor removed the tumor and inserted chemotherapy into Schade's bladder in the recovery room.

During a follow-up CT scan a year later, doctors saw no problems with Schade's bladder, but found enlarged lymph nodes in his abdomen and neck area that turned out to be cancerous, likely spread from the bladder cancer. This time, Schade was treated with systemic platinum-based chemotherapy.

A stiff neck sent Schade back to the doctor in 2015, and that, too, was diagnosed as a recurrence of cancer in his lymph nodes. Offered chemotherapy or a clinical trial with two immunotherapies, Schade recalled his treatment in 2011, which he described as "not a pleasant experience." He was working in the garage door business then, and chemotherapy's side effects, which included the loss of his hair and physical strength, interfered. "I struggled to make it into work and function normally," he says. So, in 2015, Schade chose the clinical trial, receiving a combination of Imfinzi (durvalumab) and tremelimumab for one year. Fortunately, the immunotherapy worked, shrinking his tumors, with side effects that included treatable pancreatitis and pneumonitis, both conditions caused by inflammation triggered by the immune-activating effect of the drugs.

Imfinzi is one of five immunotherapies approved by the Food and Drug Administration (FDA) for treatment in cases where bladder cancer progresses after chemotherapy. All the drugs are checkpoint inhibitors, meaning they interfere with the activity of proteins cancer uses to keep the immune system quiet so that it won't attack. The treatment allows the body to more effectively recognize and fight the disease. »



» SCHADE chose immunotherapy to treat his recurrent bladder cancer because he didn't want to repeat his unpleasant experience with chemotherapy.

Similar to the others in its class, Imfinzi was approved in 2017 to treat patients with locally advanced (inoperable) or metastatic bladder cancer experiencing disease progression after responding to initial, or first-line, treatment with a platinum-based chemotherapy. In addition, a couple of these drugs are available to patients with recurrent advanced or metastatic disease who cannot receive chemotherapy. But now, some patients have the opportunity to receive immunotherapy sooner, while they are still experiencing disease control from chemotherapy, as a means of prolonging their response.

Bavencio (avelumab), also approved in 2017 to treat disease progression or recurrence after chemotherapy, received the green light in June for use as a maintenance treatment, to be administered to patients with stable or improved disease immediately after first-line platinum-based chemotherapy for bladder cancer that, at initial diagnosis, was locally advanced or metastatic. This means that, after the completion of chemotherapy, eligible patients will no longer have to wait until their cancer returns to be considered for immunotherapy in order to lengthen or extend remission.

Metastatic bladder cancer is a challenging disease to treat, says Dr. Petros Grivas, a medical oncologist at UW Medicine in Seattle, an associate professor at the University of Washington and lead researcher of the JAVELIN Bladder 100 phase 3 trial that led to Bavencio's approval by the FDA for this maintenance use. The prognosis for those whose disease is metastatic when first diagnosed is poor, and giving patients immunotherapy treatment earlier, when their cancer has responded to chemotherapy and not yet progressed, was shown to prolong overall survival, meaning the time from the start of treatment until death, and to delay disease progression.

TREATING METASTATIC BLADDER CANCER

The most common first-line treatment for metastatic bladder cancer is chemotherapy that combines a platinum agent — cisplatin or, if the patient cannot tolerate it, carboplatin — with gemcitabine, a chemotherapy that doesn't contain platinum, Grivas says. For many types of solid tumors, including bladder cancer, this type of treatment is given for a set number of cycles, typically four to six, rather than indefinitely, as the treatment doesn't cure cancer that has spread to distant locations in the body and can cause side effects.

After receiving up to six cycles of treatment, a patient with metastatic bladder cancer continues to see the doctor for follow-up visits to monitor for cancer progression. "Unfortunately, the vast majority of patients will develop progression of their cancer, usually within a period of months," says Dr. Matthew Galsky, a medical oncologist at the Icahn School of Medicine at Mount Sinai in New York City. "It was always sort of a strange approach to stop treatment in the context of a metastatic cancer," he says, "but we didn't have anything better that would offer a favorable risk-benefit profile. Giving a treatment holiday seemed to be the best approach."

Now, patients who have stable or improved disease after completing chemotherapy can potentially receive Bavencio to maintain those health benefits.

The JAVELIN Bladder 100 trial data showed a significant overall survival benefit for patients who received Bavencio immediately following chemotherapy compared with those who did not. The median overall survival for those who received Bavencio plus best supportive care was 21.4 months, compared with 14.3 months for those in the group that received best supportive care alone. "The study showed a very significant difference in terms of overall survival, as well as progression-free survival," meaning the time from the start of treatment until disease worsened, Grivas says. It is expected that the results will change the standard of care for this population of patients. "It's really exciting news for patients and their families," Grivas says.

Under previous treatment guidelines, about 25% to

PHOTO PROVIDED BY CHRISTOPHER SCHADE

55% of patients received another therapy if their disease progressed after initial chemotherapy. A patient might not receive treatment if their cancer was progressing too quickly or they were not fit enough for treatment, Grivas says. Making Bavencio available as a maintenance treatment will allow more patients to receive immunotherapy. About 70% to 80% of patients finishing first-line chemotherapy have disease that is stable or improved, he says, and the majority of them will be eligible to receive immunotherapy. Exceptions include those who have active autoimmune disease or immunosuppression.

> **"In general, the results seem favorable enough to change practice, in my opinion. This is the largest degree of benefit in terms of overall survival that we've seen in a randomized phase 3 trial for metastatic urothelial cancer in the first-line setting."** – *DR. MATTHEW GALSKY, Mount Sinai Hospital*

NEWER STRATEGIES TO IMPROVE TREATMENT

The use of Bavencio as a maintenance treatment exemplifies an important strategy in improving care for metastatic bladder cancer: moving FDA-approved drugs to an earlier therapy phase so they can have a larger impact, Galsky says.

There are two other key approaches, he adds. One involves identifying combination regimens capable of overcoming resistance to immunotherapies given alone. The other is using biomarkers — genetic alterations specific to patients or their cancers — to better identify who should receive which treatment. Based on analyses of the number of mutations in a patient's tumor and whether the mass expresses the immune-dampening protein PD-L1, "there is some resurgence of interest in trying to better identify subgroups of patients who might do quite well with (checkpoint inhibitors) alone," Galsky says.

Not surprisingly, the five immunotherapies already approved to treat disease that flares up after chemotherapy are attractive candidates to move to an earlier treatment setting, Galsky says. In addition to JAVELIN Bladder 100, Galsky led a second trial testing that concept. The randomized phase 2 study compared the immunotherapy Keytruda (pembrolizumab) given as maintenance versus placebo after first-line chemotherapy. This strategy is called switch maintenance therapy because, when initial treatment ends, the patient is switched to a different treatment for maintenance therapy, as is done with Bavencio.

The trial met its main goal of showing better progression-free survival, as well as higher response rates, with Keytruda. While it did not show a significant overall survival benefit, which was a secondary goal, "that's probably mostly related to the smaller sample size and the fact that the study was underpowered to show a survival improvement," Galsky says. His study also allowed patients with cancer that progressed on the placebo to instead get Keytruda, known as "crossover," which may have diminished the observable overall survival benefit.

In some cancer types, such as lung cancer, chemotherapy may work better in combination with immunotherapy than it does alone in some patients, Grivas says, but that hasn't been the case with metastatic bladder cancer. In that disease, he says, chemotherapy can help shrink or control the tumor, potentially allowing the immunotherapy to work better afterward. "These are all theoretical concepts," Grivas says. "I don't think we have a good answer for why the back-to-back approach seems to work better, so far, compared to the combination approach."

One clinical trial, IMvigor130, did test chemotherapy in combination with immunotherapy to treat bladder cancer. Patients received platinum-based chemotherapy with or without the immunotherapy Tecentriq (atezolizumab) as a first-line treatment. The study showed prolonged progression-free survival but on interim analysis did not show a significant overall survival benefit, Grivas says. He is watching for longer-term follow-up results from this and several other trials testing chemotherapy/immunotherapy combinations, including CheckMate901, which is investigating the immunotherapies Opdivo (nivolumab) and Yervoy (ipilimumab) with or without chemotherapy.

BIOMARKERS TO GUIDE IMMUNOTHERAPY

The immunotherapies approved to treat metastatic bladder cancer that worsens or comes back after chemotherapy, including Bavencio, target the PD-L1 and PD-1 signaling pathways, chains of chemical reactions that send messages to cells from their environment that suppress the immune response to tumors. Targeting these pathways stops the proteins PD-L1 and PD-1 from binding together and may boost the body's immune response against cancer cells.

About half the patients in the JAVELIN Bladder 100 trial had a high level of expression of PD-L1 in their tumor, and they experienced a greater degree of overall survival benefit. However, an overall survival benefit also was seen to a smaller degree that was not statistically significant in patients with PD-L1-negative tumors, Grivas says. Because of that, he says, every patient completing platinum-based chemotherapy who has stable or improved disease should be considered for Bavencio maintenance treatment, as long as they don't have any uncommon contraindications. »

WARREN BUIKEMA, seen here at the Ishnala Supper Club in Wisconsin, had thyroid problems as a side effect of immunotherapy for bladder cancer.

Even though patients both with and without PD-L1 expression in their tumors should be offered Bavencio maintenance, "biomarkers are the holy grail," Grivas says, and many studies are looking at gene alterations that might help define which patients are best suited for immune checkpoint inhibitor therapy. Across the five immunotherapies approved for metastatic bladder cancer, "most of the studies suggest that PD-L1 expression has some ability to enrich for responses, but that hasn't necessarily informed practice in most clinical disease states of bladder cancer because of the lack of great alternative treatment options," Galsky says.

That said, the JAVELIN Bladder 100 researchers are working to identify data on different biomarkers in the tumor tissues that were examined in their trial, and they hope to present that data soon.

COMBINING BIOMARKERS

Carefully selecting patients for a specific checkpoint inhibitor is important, as these drugs have side effects, including a high cost that might not be entirely covered by health insurance. "It is extremely important to develop clinically useful biomarkers to guide treatment decisions," says Dr. Sangeeta Goswami, an assistant professor of genitourinary oncology at The University of Texas MD Anderson Cancer Center in Houston. Using initial biopsy samples to identify a tumor's genetic and immune attributes can help determine if a patient is a good candidate for a specific treatment, she says.

The rates of overall response to immunotherapies for bladder cancer, meaning the proportion of tumors that shrink or stay stable when treated, range from 17% to 25%, Goswami says. "One of the major questions is why the majority of patients aren't responding to single-agent immune checkpoint therapy," she says. According to Goswami, it's important to start looking at combinations of a tumor's genetic and immunological attributes to help predict response.

One promising biomarker is mutational burden, or a tumor's number of genetic mutations, which research shows is potentially associated with a higher response rate to immunotherapy. IMvigor130 has also shown that when patients have both high tumor mutational burden and high PD-L1 expression, they experience improved progression-free survival compared with patients who have only one of the biomarkers, or neither of them. A proportion of patients who participated in the IMvigor130 study had this combination and markedly better outcomes with checkpoint inhibitors alone versus chemotherapy, Galsky says. Patients in the IMvigor130 trial received Tecentriq plus chemotherapy, Tecentriq alone or chemotherapy alone as a first-line treatment for metastatic bladder cancer. "A combination of those two biomarkers is emerging as a potentially powerful way to predict which patients would be best suited for immune checkpoint blockade, but further validation of that is required," Galsky says.

To further parse which patients respond to immunotherapy for metastatic bladder cancer, Goswami and her colleagues used genetic sequencing data to find that patients who responded to treatment with checkpoint inhibitors in two previously conducted phase 2 trials were more likely to have the ARID1A gene mutation. This mutation is present in about 25% of patients with metastatic bladder cancer, 35% of those with endometrial cancer and 50% of those with ovarian cancer, she says. Goswami also observed that patients whose tumors had a higher expression of CXCL13, a protein involved in antibody-producing B cell immune activation, experienced improved overall survival. She hypothesized that since both biomarkers are important on their own, combining them could increase their ability to predict better treatment response. Using

PHOTO PROVIDED BY WARREN BUIKEMA

data from the same two trials, CheckMate 275 and IMvigor 21, she found that patients with both mutations experienced improved overall survival compared with those who had either biomarker individually or the absence of both.

Given that a minority of patients respond to immunotherapy, targeting the right patient, when possible, is important. "Increasing the response rate will change the landscape of treatment for these patients," Goswami says.

IMMUNOTHERAPY'S SIDE EFFECTS

While side effects occur with immunotherapy, they aren't different in the maintenance setting compared with other settings. The Bavencio side effects in the JAVELIN Bladder 100 trial were similar to those already known to be associated with immunotherapy, Grivas says, and no new safety issues were found during the trial. The most common serious side effects observed in the trial, which occurred more frequently in the group that took Bavencio, were urinary tract infection, anemia, the presence of blood in urine, fatigue and back pain. No severe side effects or deaths were reported. Diarrhea and rash are also fairly common side effects of checkpoint inhibitors.

> Every patient with locally advanced or metastatic bladder cancer whose disease responds to platinum-based chemotherapy and is stable or improved at the conclusion of treatment can be considered for immediate maintenance treatment with the immunotherapy Bavencio (avelumab), as long as they're not immunocompromised.

"These are drugs that will be used when patients progress anyway," Galsky notes, so individuals who take maintenance immunotherapy may simply experience side effects a few months earlier than they would have otherwise.

Warren Buikema, now 73, experienced some side effects after he received immunotherapy for progressive bladder cancer in 2018.

He initially received a diagnosis in 2016 after experiencing burning with urination. His first treatments consisted of surgery to remove the tumor and insertion of Bacillus Calmette-Guérin (BCG), a type of immunotherapy for earlier-stage cancer, into the bladder.

During a regular follow-up, the doctor found lesions in Buikema's bladder that weren't healing and eventually became cancerous. In 2018, Buikema entered a clinical trial, receiving a combination of chemotherapy and the immunotherapy Opdivo (nivolumab). To avoid further cancerous lesions, Buikema had his bladder surgically removed in 2019.

Likely as a result of the immunotherapy, Buikema was told, he experienced thyroid problems leading to the need for thyroid replacement medication. While the immunotherapy treatment left him feeling foggy and disconnected for a short time following its administration, he says, that side effect wasn't bad.

Despite the possibility of side effects, Galsky believes that immunotherapy maintenance treatment in patients with advanced or metastatic bladder cancer is a true breakthrough and worth strong consideration by patients and their doctors.

"In general, the results seem favorable enough to change practice, in my opinion," he says of Bavencio maintenance. "This is the largest degree of benefit in terms of overall survival that we've seen in a randomized phase 3 trial for metastatic urothelial cancer."

"This is a very exciting time in the bladder cancer area, because we've been doing chemotherapy for the last 30 to 40 years," Goswami adds. "We now have so many options. We have to make it more personalized to see how we sequence therapy and how we know what biomarkers to use for treatment."

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Reclaiming *Intimacy*

After treatment for bladder or prostate cancer, many survivors confront permanent sexual side effects. The good news is that treatments and psychological support are available.

By MARILYN FENICHEL

When John Squire was first diagnosed with bladder cancer in January 2014, he was hopeful that treatment with bacillus Calmette–Guérin (BCG) would be effective. An immunotherapy vaccine made from a bacterium similar to the one that causes tuberculosis, BCG is administered through a catheter directly into the bladder, where it comes into contact with cancer cells and prompts the immune system to attack them. The advantage of this approach is that it causes few long-term side effects.

But a year later, Squire's cancer came back, and this time the tumor had penetrated the muscular wall of the bladder. This meant he would need more intensive treatment.

"I knew I had to have my bladder removed, but I needed to decide what kind of system I wanted to drain urine," recalls Squire, 75, of Rockville, Maryland. "My options were to have the doctors construct a new bladder, have an internal pouch or an external one. I decided on the latter approach. I thought it was the simplest way to take care of urination, with the reassurance that the surgery would get rid of the cancer for good."

Yet this surgery comes with significant consequences. Dr. Trinity Bivalacqua, director of urologic oncology at Johns Hopkins Medicine, had to remove Squire's bladder, prostate and seminal vesicles. Although Bivalacqua was able to spare the neurovascular bundle, which plays a key role in supplying blood to the penis and enabling men to have an erection, the surgery nonetheless injured those nerves and the surrounding muscle. For most men, this results in difficulty having an erection, or erectile dysfunction.

Squire was no exception. He tried some of the most common interventions, such as the oral medications Viagra (sildenafil citrate) and Cialis (tadalafil) and shots administered into the penis, but the pills didn't work for him, and he didn't care for the injections. He decided not to pursue those options. »

JOHN SQUIRE AND JEAN SOMMERFIELD maintain a fulfilling physical relationship despite the sexual side effects of his surgery for bladder cancer.

"For me, a traditional sex life wasn't the be all and the end all," Squire says, "and that was true for my partner, Jean Sommerfield, as well. But we've been able to find other ways to give each other physical pleasure. Importantly, I've been cancer-free for five years. I'm happy that I was given another chance at life."

While Squire has adjusted well to the changes he's faced, male and female sexual problems that arise from treatment for bladder cancer, as well as those experienced by men after prostate cancer therapy, can create lasting challenges for many survivors. Sexual dysfunction that may be temporary can develop after chemotherapy or radiation, and nerve damage from surgery can cause long-term effects. Men treated for prostate cancer with testosterone-suppressing drugs also experience sexual dysfunction. And while the problem is treatable with a variety of strategies, it is not always reversible. Only about half of men who undergo a nerve-sparing cystectomy, or removal of the bladder, recover their natural erectile function after two years, according to Bivalacqua.

Developing self-acceptance and adopting open communication with partners and new strategies for intimacy can help survivors acclimate to these changes. Fortunately, there is a lot of support available.

TREATING ERECTILE DYSFUNCTION

According to the American Cancer Society, in the United States, about 191,930 men are likely to be diagnosed with prostate cancer in 2020, while 62,100 men may receive a diagnosis of bladder cancer. That means 254,030 men may face treatment, along with its accompanying side effects.

> **"Even with nerve-sparing surgery, the impact on sexual function is immediate. Depending on the man's age and erectile status before surgery, it may take between three and six months for some function to start coming back, and a year or two for a maximal recovery of erection."** — *DR. RUN WANG, UT Health*

Cystectomy is typically performed in patients with stages 2 to 4 bladder cancer, and radical prostatectomy, meaning removal of the prostate and surrounding tissues, is performed in men with stages 2 or 3 prostate cancer.

"Whether a man has his prostate removed to treat prostate cancer or his bladder and prostate taken out to

JOHN SQUIRE AND JEAN SOMMERFIELD PHOTOGRAPHED BY TAMZIN SMITH

treat bladder cancer, the impact is going to be very similar," explains Dr. Run Wang, a urologist with UT Physicians/ McGovern Medical School at UTHealth and The University of Texas MD Anderson Cancer Center in Houston and an expert on sexual function following cancer treatment. "Even with nerve-sparing surgery, the impact on sexual function is immediate. Depending on the man's age and erectile status before surgery, it may take between three and six months for some function to start coming back, and a year or two for a maximal recovery of erection." Even then, not all men get their sexual function back.

Wang points out that it's important to resume sexual activity as early as possible following surgery. "By engaging in some activity, even masturbation, blood flow to the penis is increased, helping to preserve the tissue and improving the likelihood of achieving erections," he says. To help restore function through temporary methods that allow more immediate sexual activity, he adds, "between 80% and 90% of men in my practice do choose some intervention following surgery."

For most men, pills are usually the first treatment option, but often they are not enough. At that point, many men try penile injections, which they learn to administer themselves, before they want to have intercourse. One medicine or a combination of several are injected into the penis. According to Bivalacqua, if the surgery was done properly, injections should result in functional erections.

If both of these interventions fail, men may consider a penile prosthesis. This device must be surgically implanted and consists of a reservoir of saline, two cylinders and a pump. When a man presses the pump, the saline flows into the cylinders, causing an erection. This device is highly effective, working for most men who use it.

Nonetheless, most men experience some depression as they come to terms with the changes in their bodies. "To avoid some of the emotional shock, men and their partners should be educated before surgery about what to expect in terms of sexual function," Wang says. "For example, men should be told that their erections won't be as firm, and when they have an orgasm, they will not have ejaculate. Surprisingly, some young men are unaware that the surgery will make them infertile, so that, too, has to be made clear. Another thing many men don't know is that they can sometimes have an orgasm without an erection, usually by masturbating. Having this information on hand and being prepared for these changes helps in the recovery process, as does therapy and sexual counseling with a trained professional."

CHALLENGES FOR WOMEN AND MEN

Both men and women can get bladder cancer, although it is more common in men. In addition to the 62,100 men who will likely be diagnosed in 2020, about 19,300 women will receive this diagnosis. Regardless of gender, once the cancer invades the bladder's muscular wall, surgery is usually the treatment of choice. Part of the surgery involves developing a new system for draining urine. Options include an ileal conduit, which includes an external pouch; an internal pouch called a continent cutaneous pouch; or a neobladder, constructed from part of the small intestine. There are pros and cons to each approach.

Squire opted for the ileal conduit, which involves having a stoma, or opening, created in the abdomen with an ostomy bag placed over it. He thought this approach would be the easiest to manage. "The internal pouch felt complicated because I would have had to use a catheter to drain it every few hours," he says. "And, I heard that there was a lot of incontinence with the neobladders. The option I chose works well, though initially my ostomy bag leaked. I quickly discovered that the problem was that I wasn't using the right kind. Once I fixed that, I haven't had any problems."

Dr. Mohit Khera, a urologist at Baylor College of Medicine in Houston, notes that, for some men, having an ostomy bag can affect sexual function psychologically. "They may feel disfigured," he says. "For this reason, a majority prefer a neobladder, but there are potential side effects associated with this approach. Urinary tract infections are pretty common, as are stones in the bladder and scarring of the ureters going into the neobladder."

With the urinary issues addressed, both men and women have to adjust to the changes in their bodies as they consider resuming a sexual relationship with their »

3 QUESTIONS TO ASK YOUR DOCTOR

- ☐ I'M SCHEDULED TO undergo chemotherapy and/or radiation for prostate cancer or bladder cancer. What are the sexual implications, and can you take any measures to preserve my sexual function?
- ☐ I'VE BEEN TOLD THAT I need surgery for my bladder cancer or prostate cancer. Will you do a nerve-sparing surgery to help prevent permanent sexual dysfunction?
- ☐ I'M A WOMAN SCHEDULED FOR cystectomy. Will you be able to leave my vagina intact to preserve my ability to have intercourse?

New Treatments for Erectile Problems on the Horizon

FOR THE PAST FEW YEARS, researchers have been working on innovative therapies that may represent more durable treatment options for erectile dysfunction. The most promising is shockwave therapy, which involves sending high-energy sound waves directly to the penis in a pain-free procedure. The therapy stimulates growth of new blood vessels and possibly breaks down plaque build-up in existing vessels. Baylor College of Medicine's Dr. Mohit Khera has been involved in this research, and the findings have been encouraging.

"Our results show that if we apply 2,500 shocks per week, it can help some men," he says. "But there are still many questions about how often to administer the treatment and what is the optimal dose." Khera adds that some preliminary work is underway to test this therapy for women.

Stem cell therapy is another treatment under investigation. The technique used at Baylor is to harvest stem cells from the abdomen and inject them directly into the penis. The stem cells repair damaged blood vessels.

Clinical trials have found that the treatment wears off over time, possibly requiring another injection at that point.

Khera's team soon will be testing another use of stem cell therapy — administration immediately after a radical prostatectomy to prevent erectile dysfunction altogether. "In the laboratory, erectile function in a rat nerve-injury model does improve following stem cell treatment," he says. "We'll see what impact this approach has when we begin our clinical trials with men."

partners. Just as men will need assistance getting an erection, women sometimes have to deal with the ramifications of having their uterus and ovaries removed. In some instances, the vaginal wall, where the bladder sits, also may need to be removed, although doctors try to avoid taking out these organs whenever possible so that intercourse will remain possible. Significant changes result from surgery, many of which have a direct impact on a woman's sex life.

"Not only do women experience vaginal dryness, they also may have pain during sex," Khera says. "If women have an ostomy bag, they may experience poor self-image, leading to a lack of desire. Fortunately, there are remedies to address these problems."

Jeanne Carter, head of Memorial Sloan Kettering's Female Sexual Medicine and Women's Health programs in New York, concurs, emphasizing that the first step is seeking help for sexual difficulties. "A woman may come alone or with a partner, and during the initial consultation, we talk about her needs and concerns in a safe, comfortable environment," Carter says.

Addressing vaginal dryness and the pain and discomfort it causes is often the place to start. "Many women don't realize that there's a difference between moisturizers and lubricants," Carter explains. "Nonhormonal moisturizers are for tissue quality and come as gels, creams or suppositories. For patients with cancer and survivors, they can be applied as often as three to five times a week for symptom relief and to maintain vaginal health. Lubricants are liquids or gels that are applied for sexual touch or vaginal insertion to decrease friction and enhance enjoyment. Both complement each other and are used for different reasons."

For women experiencing vaginal tightness — another common problem that arises after surgery — dilators use a simple device that can help tremendously.

"We recommend dilators, cylinder devices used to stretch the vagina," Carter says. "They come in different sizes and can help women learn how to relax pelvic floor muscles. A smaller dilator can help reduce pain before a vaginal exam, while a larger one works to prepare the vagina for penetration. They can go a long way in reducing discomfort and building a woman's confidence about intimacy and future exams."

Coupled with these approaches, Carter also suggests that women do pelvic floor exercises, called Kegel exercises. They involve tightening the pelvic floor muscles for three to five seconds and then relaxing them for an equal amount of time, repeating until muscle fatigue sets in. These exercises are easy to do and can help women learn how to control these muscles.

Finally, two medications approved by the United States Food and Drug Administration are available to help women who have a decreased interest in sex. Addyi (flibanserin) is a pill that acts on brain chemistry to stimulate desire. It must be taken every day. Vyleesi (bremelanotide), an injection that is administered before intercourse, also targets the brain's hormones to activate desire. Women should be aware, however, that according to the National Women's Health Network, the clinical trials included mostly White women, and the medications were effective only for a relatively small number of women — between 8% and 13% for Addyi, and 8% for Vyleesi. In addition, there are side effects associated with the drugs. The most common with Addyi are dizziness, sleepiness, nausea, fatigue, insomnia and dry mouth, and with Vyleesi, the most common are nausea and vomiting, flushing, injection site reactions and headache.

> **“Having a supportive sexual partner is essential. If both partners encourage each other, there’s a good chance that they can find a way to be successful.”** — *DR. MOHIT KHERA, Baylor College of Medicine*

PSYCHOLOGICAL READINESS IS KEY TO INTIMACY

Having a fulfilling sexual relationship involves more than addressing the changes to the body resulting from treatment. Both men and women need to be psychologically ready, as well, which often means coming to terms with the ordeal they have been through. Daniela Whittmann, a clinical social worker, certified sex therapist and associate professor of urology at the University of Michigan in Ann Arbor, points out in a webinar presented under the auspices of the Bladder Cancer Advocacy Network that women need to go through a period of grieving for what they have lost before they can begin to build a new kind of sexual relationship. Whittmann stresses that intimacy will be different but can be just as satisfying.

Khera agrees, adding that what he calls the four pillars of health — diet, exercise, sleep and stress reduction — can make a big difference. “Vigorous exercise 90 minutes a week, getting seven hours of sleep each night and reducing the stress in your life can help improve an individual’s desire for sex,” he says. “And above all, avoid smoking, which can significantly increase the risk of many kinds of cancer, including bladder cancer.”

Perhaps the most important part of recovery for both men and women is communication. A couple needs to talk about what they are looking for in their sexual relationship, what new ways they can give each other pleasure and how they can continue to reinforce their emotional intimacy.

Khera adds that setting new expectations and goals is a key part of the recovery process. “Having a supportive sexual partner is essential,” he says. “If both partners encourage each other, there’s a good chance that they can find a way to be successful.”

Some couples learn to redefine intimacy. “John and I find deep satisfaction with emotional intimacy, traveling together, spending time together and enjoying each other’s company at home,” says Sommerfield, 72, Squire’s partner of seven years. “John and I have maintained a fulfilling physical sexual relationship. We continue to give one another physical pleasure, just not through traditional intercourse. We know that cancer doesn’t stop your life. In fact, it has made us both — and our relationship — stronger.” C


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Going Another Round

Primed to knock out cells vulnerable due to DNA-repair problems, PARP inhibitors are ushering in a targeted-drug era in prostate cancer treatment.

By LEAH LAWRENCE

Daryl Elzy, 60, an Air Force retiree from North Carolina, has been living with prostate cancer for about 12 years and has been a participant in clinical trials almost as long.

"Every time they offered me a trial, I said, 'Sign me up!'" Elzy says.

Earlier this year, Elzy completed a clinical trial — his third — testing PARP inhibitors, a class of drugs that is new to the treatment of prostate cancer. PARP is an enzyme in cells that helps repair DNA when it becomes damaged. The inhibitors can block PARP in cancer cells, keeping them from repairing their damaged DNA and causing them to die.

PARP inhibitors were first approved by the United States Food and Drug Administration (FDA) in 2014 to treat certain ovarian cancers and, more recently, to treat breast cancers. In May, two PARP inhibitors became the first in their class approved as therapies for certain metastatic prostate cancers, ushering in a new era of treatment with targeted drugs. While drugs that suppress the hormones that fuel metastatic prostate cancer are the mainstay of treatment, PARP inhibitors can help certain patients whose disease has become resistant to those medications.

In particular, the patients most likely to benefit from PARP inhibitors are those who have tumors with DNA repair defects. It is for those patients that Lynparza (olaparib) and Rubraca (rucaparib) are intended.

"Our bodies have mechanisms in place to repair damage that happens to our DNA," explains Dr. Veda N. Giri, director of cancer risk assessment and clinical cancer genetics at the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia. DNA damage happens on a daily basis and can be caused by things such as exposure to ultraviolet light, radiation, cell turnover or substances in the environment. »

> **“Every patient with advanced prostate cancer, and particularly metastatic castration-resistant prostate cancer, should discuss with their oncologist the role of tumor genomic testing and if they qualify for (PARP inhibitors), the timing of treatment and what to expect in terms of side effects.”**
>
> *— DR. MAHA HUSSAIN, Robert H. Lurie Comprehensive Cancer Center*

“DNA houses genes that act as the control center for our cells and tell the cells what to do,” Giri says. “If DNA is damaged in the region that houses those genes — called DNA repair deficiency — it can lead to improper signals and result in disease conditions such as cancer.”

ONE-TWO PUNCH

Mutations in DNA repair genes can be acquired, meaning that the mutation develops in the tumor as it grows, or they can be inherited, meaning that the glitches are present throughout the body in all of a patient’s cells. “Reports state that about 25% to 30% of men with metastatic prostate cancer have acquired, tumor-only DNA repair deficiency mutations, and about 12% to 17% of men have inherited mutations,” Giri says. “For men with earlier-stage prostate cancer, about 5% to 7% have inherited mutations.”

Among the most common DNA repair deficiency mutations are BRCA1 and BRCA2 gene mutations and a mutation in ATM, a “BRCA-like” gene also involved in DNA repair, Giri says.

DARRYL ELZY BY SEASON MOORE

Genetic Testing for Prostate Cancer

In 2019, an international panel of experts met at the Philadelphia Prostate Cancer Consensus Conference to address which patients with the disease should undergo genetic testing. Its findings were published to help guide physicians and their patients.

Who Should Receive Genetic Testing?

- All men with metastatic prostate cancer
- Men with nonmetastatic prostate cancer, if they have:
  - Ashkenazi Jewish ancestry.
  - Advanced disease.
  - Intraductal/ductal pathology.
  - Grade 4 or higher disease.
- Men with a family history, meaning those whose father, one brother or two or more male relatives:
  - were diagnosed with prostate cancer at age 60 or younger,
  - died of prostate cancer,
  - and/or had metastatic prostate cancer.
- Men with a family history of other cancers if:
  - two or more cancers in the hereditary breast and ovarian cancer or Lynch syndrome spectrum have been diagnosed in relatives on the same side of the family, especially if they received their diagnoses at age 50 or younger.

What to look for?

The panel suggested using tests that look for myriad mutations but include screens for priority genes associated with metastatic disease, including BRCA2, BRCA1, mismatch repair genes and possibly the ATM gene, because that could indicate eligibility for a clinical trial. In addition, any genes associated with a man's family history of cancer should be included.

The same genes should be looked for in tests of prostate tumor tissue, which should be conducted in all men with metastatic disease, the panel agreed. Testing of these genes also may be performed in men with nonmetastatic disease, particularly as a way to guide active surveillance, the experts wrote.

For men with affected relatives but no cancer, the panel recommended testing for mutations to BRCA2, HOXB13, BRCA1, ATM, DNA repair genes and those associated with family history. In addition, based on results of the PROfound study of Lynparza (olaparib) in prostate cancer published in May 2020, men who do not have BRCA1 or BRCA2 mutations may respond to PARP inhibitors. That's why Dr. Maha Hussain, deputy director of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University's Feinberg School of Medicine in Chicago, recommends that a broader test panel be considered, as this could provide opportunities for patients who do not have the required mutations for PARP inhibition but may have other mutations that qualify them for clinical trials.

When to screen for cancer?

For men with a BRCA2 mutation, screening for prostate cancer should begin at age 40 or 10 years before the youngest diagnosis of the disease in the family. This should also be considered for men with mutations to the HOXB13, BRCA1 or ATM genes and those with mismatch repair deficiencies.

DNA repair deficiencies affect signaling pathways, strings of chemical reactions that pass messages to a cell from its environment about how to behave. Pathways are associated with proteins encoded by specific genes.

When cancer cells have a DNA repair deficiency in the BRCA pathway, for example, the cells adapt and use an alternative pathway to repair themselves. PARP is one of those pathways. Using PARP inhibitors in patients who have an existing DNA repair deficiency delivers a one-two punch (known in scientific terms as "synthetic lethality") to the cancer cells, which leads to cell death.

NEW TO PROSTATE CANCER

The exact percentage of men with DNA repair mutations who will benefit from these drugs is still being established, according to Dr. Joshua M. Lang, associate professor of hematology, medical oncology and palliative care at the University of Wisconsin School of Medicine and Public Health in Madison. That is because, for many years, it was thought that genetics were not as important in prostate cancer as in other cancers.

"Fundamentally, this is all a new area in prostate cancer," Lang says. "In the last five years, we have become aware of genetic changes associated with prostate cancer not just in the tumor cells, but also in genes that can be inherited."

Previously, the majority of genomic testing was done in samples taken during prostatectomy, meaning the surgical removal of the prostate, Lang explains. While inherited mutations can be found through tests of blood, saliva or tissue samples, experts are learning that acquired »

“The (PARP inhibitor) that I am on now has helped me significantly. Before I took this drug, I was in a lot of pain and was regularly having to take oxycodone. On this drug, within about a month, the pain went away and I was able to get off oxycodone.”

— PATRICK MCGUIRE, patient

PATRICK MCGUIRE stands at Denali National Park in Alaska about 10 years ago, before he was treated for cancer.

mutations — the ones that occur in the cancer as it grows — are not always present in the prostatectomy sample and may only appear later in biopsies taken from metastatic sites.

Elzy received a diagnosis of prostate cancer when he was 48. Although the average age at diagnosis is about 66, men found to have an inherited BRCA2 mutation are more than four times as likely than those without the mutation to receive a diagnosis before that age. Compared with men who don't have the mutation, the risk of prostate cancer is more than eightfold higher for men who have the BRCA2 mutation and are 65 or older.

Elzy was initially treated with radiation and a prostatectomy to remove the tumor.

“My doctor realized that a portion of my cancer was outside of the margin of being able to remove it, so I knew that there was still the possibility of lingering tumor that we couldn't reach,” Elzy says.

To address the lingering cancer cells, Elzy underwent chemotherapy, but his blood level of the protein prostate-specific antigen (PSA) — which often rises in response to the growth of prostate cancer — continued to increase. That is when his physician began to look for clinical trials.

“My first two trials both had good results to start, but all of a sudden the PSA would start rising again,” Elzy says.

Eventually, his doctor decided that Elzy should be sent for genetic testing. The National Comprehensive Cancer Center now recommends that all men with metastatic prostate cancer undergo blood tests to determine if they have inherited DNA repair deficiency. Testing can also be done on tumor samples to look for acquired mutations.

Elzy's results revealed a BRCA2 mutation that his doctors suspect he inherited from his mother, who died of breast cancer in 1992. If genetic testing had been more advanced back then, Elzy, who has no siblings or children, likely would have been advised to undergo genetic testing to find out if he had inherited the mutation.

Dr. Maha Hussain, deputy director of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University's Feinberg School of Medicine in Chicago, noted that, at the moment, having information about inherited mutations does not change the initial approach to treating newly diagnosed prostate cancer. Similarly, knowing a patient is BRCA-negative when newly diagnosed does not eliminate the possibility that the tumor will acquire a mutation as it grows.

“This could all change as our knowledge improves,” Hussain says. However, in her practice, Hussain says she has begun to send tissue for testing in men with high-risk,

PHOTO PROVIDED BY PAT MCGUIRE

hormone-sensitive disease or prostate cancer that has recently stopped responding to hormone-suppressing drugs. "Getting prepared and ahead of the game is the best approach," she says. "Clearly, testing for germline has implications for blood relatives, and I offer patients the opportunity."

In Elzy's case, once he learned that he had an inherited mutation, he was quickly recruited into a clinical trial of a PARP inhibitor.

AVAILABLE TREATMENTS

Lynparza and Rubraca are the only PARP inhibitors approved by the FDA so far for men with metastatic castration-resistant prostate cancer (mCRPC), meaning disease that has spread beyond the prostate and has progressed on hormone-suppressing treatments. Lynparza is approved to treat men with cancer that progressed after treatment with one of two hormone-based prostate cancer therapies, Xtandi (enzalutamide) or Zytiga (abiraterone). To be eligible, patients must have a mutation in one of the homologous recombination repair (HRR) genes, specifically BRCA1, BRCA2 or ATM, which constitutes a DNA repair deficiency. Patients can be selected as good candidates to receive the therapy based on the results of an FDA-approved companion diagnostic for Lynparza.

Rubraca is approved for men with mCRPC and a BRCA1 or BRCA2 mutation who have received treatment with androgen receptor-directed therapy and a taxane-based chemotherapy.

Lynparza was approved based on the results of a clinical trial comparing the drug against Xtandi or Zytiga. Men with BRCA1, BRCA2 or ATM mutations were assigned to treatment with Lynparza, while men with any of 12 other mutations associated with HRR were given Xtandi or Zytiga. Men treated with the PARP inhibitor went twice as long before experiencing disease progression (7.4 months versus 3.6 months), and early data showed that their overall survival was nearly five months longer than those in the group that received hormonal treatment (19.1 months versus 14.7 months). In patients who had tumors that could be measured, about one-third of those who received Lynparza saw their tumor respond to the drug compared with only 2% of men treated with the other drugs. When looking at all the men in the study, including those with mutations other than BRCA or ATM, a meaningful delay in disease progression was observed among those who took Lynparza compared with investigator's choice of treatment (5.8 months versus 3.5 months).

Response to Lynparza also may vary depending on the type of mutation, with the phase 2 TOPARP-B study showing that 80% of patients with a BRCA1 or BRCA2 mutation responded to the treatment while 37% of patients with ATM mutations responded.

Rubraca was approved based on the results of a trial in which all patients received the PARP inhibitor and a hormone-suppressing drug. In this study, 42% of the men who participated saw their tumor respond to the drug.

"There are many ways to assess response, including the rate of PSA decline, the shrinkage of tumors and delaying cancer progression," Hussain said. "Based on the PROfound trial, the odds of response to Lynparza as measured by PSA decline of 50% or greater was seen in 43% who had BRCA1, 2 or ATM mutations compared with 8% (six of 77) in the patients who received Zytiga/prednisone or Xtandi. In the overall study population, a PSA response was confirmed in 30% in the Lynparza group compared with 10% in the control group. The data also show benefit in terms of significantly delaying pain progression, which is a critical point from a quality-of-life perspective."

TUMOR RESPONSE

Patrick McGuire, 73, a retired scientist from Wisconsin, has benefited from PARP inhibitors. McGuire received a diagnosis of prostate cancer in October 2015. After undergoing prostatectomy, he learned he had metastatic disease and began to participate in clinical trials. Like Elzy, he found that each trial led to only a temporary improvement in his disease.

Throughout his time in clinical trials, McGuire had been providing blood samples for testing, and after his cancer progressed during the first two trials, Lang had him undergo genetic testing, which revealed a BRCA2 mutation. McGuire did not disclose whether the mutation was acquired or inherited. Lang helped McGuire enroll in a clinical trial testing the combination of Zytiga and a PARP inhibitor.

"The drug that I am on now has helped me significantly," McGuire says of the PARP inhibitor. "Before I took this drug, I was in a lot of pain and was regularly having to take oxycodone. On this drug, within about a month, the pain went away, and I was able to get off oxycodone."

Prior to his cancer diagnosis, McGuire and his wife loved to travel, fish, hike and camp. For years, McGuire was no longer able to enjoy these activities, but treatment with the PARP inhibitor has allowed him to start participating again.

Like most cancer treatments, PARP inhibitors do cause some side effects. McGuire says he experiences shortness of breath, which was helped by a dose reduction; the drug also affected his red blood cell production. Other common side effects of these drugs include anemia, nausea, fatigue, decreased appetite, diarrhea, vomiting, cough, rash, constipation and low platelet levels.

It is important that patients discuss these side effects with their physicians, Hussain says.

"When I start someone on these drugs, I try to see them within a few weeks of initiating treatment," she says. "I want to evaluate them and make sure there are no major side effects. If there are, the earlier we intervene the better the chance of sustainability of treatment."

While on a PARP inhibitor, Elzy says, he experienced nearly no side effects. But unlike McGuire, who is still »

taking his PARP inhibitor, Elzy has moved on to his next treatment.

"It lowered my PSA level to about 0.3 and it stayed like that for maybe four to five months, but in the last three weeks, my PSA level started going upward bound," Elzy says of the PARP inhibitor. "That is when the drug was stopped."

MANY QUESTIONS REMAIN

Because PARP inhibitors are so new in the treatment of prostate cancer, many questions about the drugs are still being explored. For example, it is unknown if men without DNA repair mutations might benefit from the drugs. It is also unclear if men with inherited versus acquired mutations benefit more from one PARP inhibitor than another.

"Right now, it seems that some patients who have inherited mutations have cancers that are more sensitive to PARP inhibitors and see long-term response that potentially lasts more than a year," Lang says. "For those patients whose mutation is only in the tumor, we still see a benefit for the majority of patients, but whether that is going to last for more than a year is less certain."

While the trials that led to the approval of Lynparza and Rubraca showed significant improvements in survival, Lang and other researchers want to find out if they can do better.

"We are just at the tip of the iceberg in terms of developing PARP inhibitors and other therapeutic strategies around this class of medications," Lang says.

For example, researchers are looking into the possibility of combining PARP inhibitors and immunotherapy. There are also trials exploring combining PARP inhibitors with other treatments that target DNA damage repair, including radiation therapy.

"Combining treatments that target DNA in the cancer cell might be its own way to improve disease control and potentially knock aggressive cancers back for many years," Lang says.

Another strategy being explored is the combination of PARP inhibitors with Zytiga as an initial treatment for mCRPC. The role of PARP inhibitors alone or in combination with other drugs is also being evaluated for use earlier in the disease, before the metastatic stage. Another question involves the role of platinum, a DNA-damaging agent used in some chemotherapies, as an alternative to PARP inhibitors, Hussain says. There are several case series suggesting potential benefit, though there are no data from a large, prospective clinical trial yet.

Finally, the whole field is faced with the challenge of ramping up testing for mutations in men with prostate cancer, some of whom may benefit from a referral to a genetic counselor to discuss familial risk.

"Now there are thousands and thousands of men who need testing, and it will take a lot of hard work to catch up," Lang says. "We also face a national shortage of genetic counselors, so the field isn't entirely prepared, but hopefully we will see improvements in the coming years."

PATIENT RESOURCES

Experts agree that more genetic and genomic testing for men with advanced prostate cancer is likely taking place at major academic centers compared with community cancer centers. It is important that men are educated about genetic and tumor genomic testing, their implications, timing and whether they are eligible.

"Every patient with advanced prostate cancer, and particularly mCRPC, should discuss with their oncologist the role of tumor genomic testing and if they qualify for these treatments, the timing of treatment (and) what to expect in terms of side effects," Hussain says. "Do not turn to the internet unless it is sources of information that are well-vetted."

Throughout his treatment, McGuire turned to the Prostate Cancer Foundation, which was active in the funding of studies that helped reveal the role of inherited mutations in prostate cancer. Its website, pcf.org, offers information and resources about genetic testing.

FORCE (Facing Our Risk of Cancer Empowered) is an organization established to improve the lives of individuals and families affected by hereditary breast, ovarian and related cancers. This includes prostate cancer, and the organization's website, facingourrisk.org, includes information on the disease and the genetic mutations that might increase someone's risk of developing it.

Elzy and McGuire have faced their diagnoses with the steadfast help of their wives and with a positive attitude.

"I always say, 'I have cancer, but cancer doesn't have me,'" Elzy says. "I can't let it consume me. When I was diagnosed in 2008, my first doctor told me to get my affairs in order, and I'm still here."

They both credit participation in clinical trials for extending their lives.

"If you have metastatic cancer, I tell people to go find a doctor and a hospital you have confidence in and participate in clinical studies," McGuire says. "In my view, these trials have basically saved my life."

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Gaining Control

A growing number of treatments are available to men whose prostate cancer has spread and become resistant to hormonal therapy.

By BETH FAND INCOLLINGO

WHEN A MAN RECEIVES a diagnosis of prostate cancer, Dr. Charles Ryan has two immediate questions: Has it spread outside of the prostate and, if so, is it resistant to the hormonal therapy typically used to treat the disease?

"When we talk about a patient with a life-threatening form of prostate cancer, those are typically patients who have both of those phenomena," said Ryan, director of the Division of Hematology, Oncology and Transplantation at the Masonic Cancer Center of the University of Minnesota in Minneapolis. "The cancer spreads to the bone, and standard hormonal therapy stops being effective, so the cancer begins to grow despite the lowering of testosterone."

While those cancers, known as castration-resistant or hormone-resistant, represent the most advanced stage of the disease, the good news is that there are numerous ways to treat such cases, Ryan told *CURE*® in an interview. "In fact," he said, "the number of treatments for prostate cancer has really exploded in the last four or five years, and it's actually going to get even bigger in the next few."

Q ***CURE*®: What kinds of therapies are available to treat prostate cancer that has spread?**

A **Ryan:** We can divide them into three or four categories. With hormonal therapy, the standard of care would be some form of ablation of the level of testosterone in the body (because testosterone fuels the cancer). We typically do this with injections that lower the level of testosterone by about 90%. The most commonly used drugs would be leuprolide (Lupron Depot), degarelix (Firmagon) and goserelin (Zoladex). On top of that, we have targeted hormonal therapies that block the effect of testosterone even when the first line of therapies has failed. And that's where we have drugs like enzalutamide (Xtandi), abiraterone (Zytiga), apalutamide (Erleada) and darolutamide (Nubeqa).

Compared with some other cancers, we use relatively little chemotherapy, but we do have some very effective chemotherapies. Docetaxel can be used in advanced hormone-resistant disease or as an initial therapy for metastatic disease. And we have a drug called cabazitaxel, which is similar.

The new class of drugs that we're using now is the PARP (poly-ADP ribose polymerase) inhibitors, which target the mechanism of DNA repair (making it harder for cancer cells to repair themselves when damaged; these are used in patients whose cancers are already deficient in this ability due to gene mutations). In addition, we have a cellular therapy called sipuleucel-T, which is used in castration-resistant, metastatic disease. Finally, we have a radioisotope called radium-223, which is used in disease that has spread to the bone, causing bone pain.

Q **Do patients have trouble sticking with any of these regimens, and, if so, what kinds of problems can that cause?**

A Treatment adherence has to do with whether the prescribed medication actually gets into the patient. Adherence for injected drugs is, of course, high; if a patient shows up and has the drug injected, adherence is almost 100%. But with oral drugs, we can lose adherence for a number of reasons. One is that a patient could take a bottle of pills home, put it in his medicine cabinet and never take it. Or, it could be that a patient starts to take a medication and because he doesn't feel so good, he stops taking it. We would want to hear »

DR. CHARLES RYAN is a professor of medicine, director of the division of hematology, oncology and transplantation and the B.J. Kennedy Chair in Clinical Medical Oncology at the University of Minnesota Medical School. He treats patients who have genitourinary cancers, with a special focus on prostate and testicular cancers.

> **"But the reality is that all the research in the world that leads to the development of a new therapy isn't effective if we don't get it into the patient. So, it's sort of a dialogue between the doctor and the patient about what can or cannot be administered and why."**
>
> *— DR. CHARLES RYAN, Masonic Cancer Center of the University of Minnesota*

PHOTO COURTESY OF THE UNIVERSITY OF MINNESOTA

about that, why he doesn't feel well and whether we could reduce the dose or give him a treatment break. As oncologists, that's our job.

But the reality is that all the research in the world that leads to the development of a new therapy isn't effective if we don't get it into the patient. So, it's sort of a dialogue between the doctor and the patient about what can or cannot be administered and why. It may not be just one factor. Unfortunately, a problem in this country is that patients sometimes bear a lot of the cost of their medication, so not being able to pay would be one (reason) for a patient not adhering to the treatment regimen. And that is something that I, as a doctor, would want to hear about, because we can think about patient assistance programs if they exist in your area, or we can think about ways we can reduce the dose to allow us to effectively deliver the drug, but perhaps on a slightly more cost-effective schedule.

Q How do treatment side effects impact quality of life for patients?

A The major driver of quality of life in advanced prostate cancer is the efficacy of the therapy, and this has been shown, for example, with chemotherapy. Many men might think, "Well, chemotherapy is going to be associated with a very poor quality of life." But that didn't bear out in a study that was done many years ago, in which patients (newly diagnosed) with metastatic disease were treated with standard hormonal therapy with or without chemotherapy. The patients who were on the chemotherapy had a slightly lower quality of life after about three months of treatment, but after 12 months of starting treatment, the patients who had received the chemotherapy had a better quality of life. And that was because 12 months after starting the treatment, the patients had already been done with the treatment for six months. They were less likely to have their cancer worsening, and better cancer control leads to better quality of life.

Q What treatments are being tested in clinical trials that might eventually become options for men with advanced prostate cancer?

A I would put clinical trials into one of two categories. The first would be optimization studies using therapies that exist, but maybe we're testing them in an earlier disease population, or looking for a better outcome by giving it to a patient with a lower volume of disease.

For example, there are studies of enzalutamide and abiraterone, commonly used drugs that, when first approved, were given to patients who had received all (available) prior therapies and chemotherapy. But then we showed that we could give them to patients with castration-resistant prostate cancer who did not have chemotherapy, and then to patients (who were) newly diagnosed, and the outcomes were better than giving standard hormonal therapy alone. Now, studies are looking at patients who do not have metastatic disease. This is where we're going with prostate cancer therapies: Optimizing their use, moving them earlier in the disease spectrum and maybe changing doses.

The next type of clinical trial would be (one that uses) new therapies and new approaches. One would be the PARP inhibitors, which are relatively new. The two that are approved currently are called Lynparza (olaparib) and Rubraca (rucaparib).

The second category that's really exciting is PSMA (prostate-specific membrane antigen)-targeted therapies, and we have one that's looking really interesting. It's a molecule that targets PSMA (a protein in prostate cancer cells that fuels the disease), which arises from a very common mutation of a gene called PTEN. On one end, the treatment binds the PSMA, and on the other end, it has a sort of molecular basket. In this basket, you can put a molecule: In this case, it's the radioisotope lutetium-177. The targeted treatment sort of hand delivers the radiation therapy to the prostate cancer cell. And that looks really interesting and could get FDA (Food and Drug Administration) approval in the next few months or year.

There's another less-known, genetic-based therapy being studied, a drug that targets a molecule called AKT (generated by a fairly uncommon) mutation. If that mutation is there, then this AKT is activated and stimulating the cancer, and the drug blocks it. We might hear data on that in the coming year, and it could become available, most likely, in the advanced castration-resistant metastatic setting.

Q What will all this progress mean to patients?

A We started maybe 20 years ago thinking about this idea of personalized medicine and targeted therapies, and we're kind of there. We're not quite there totally, because we're not at the point where every patient has some unique profile that leads to a special cocktail of treatment. I think that's still a little bit far off, but we are seeing the beginning of this process.

Q If patients want more information or support, where can they turn?

A I would first recommend that patients go to the website of ZERO – The End of Prostate Cancer (**zerocancer.org**). ZERO is not only an informative website, it's also an advocacy organization. ZERO also has an annual meeting that patients can attend. I've spoken at it the last couple of years, and I have a number of colleagues who have, and there's a lot of information there.

I would also recommend looking at the National Cancer Institute's website (cancer.gov/resources-for/patients). They have a thing called PDQ, patient data query, which is a very dry presentation of patient outcome data, but can be helpful for making decisions. And then, finally, the Prostate Cancer Foundation (**pcf.org**), which is a group that I've worked with. They have patient materials that one can order, such as a cookbook for patients with prostate cancer and other things that can help them address lifestyle issues in a way that might be helpful for their long-term health.

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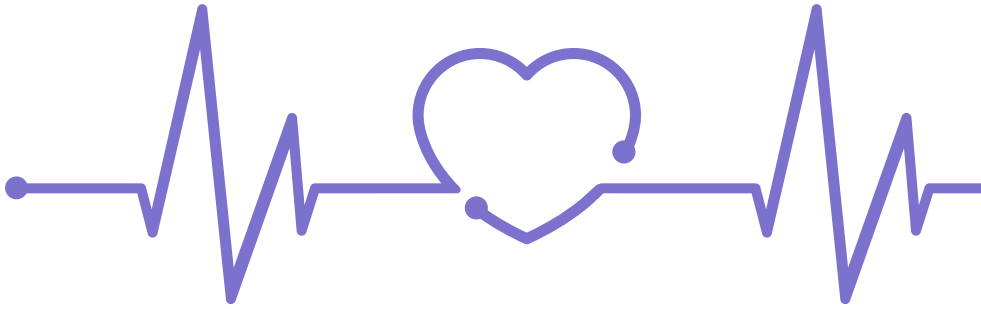

Easier on the Heart

For men with advanced prostate cancer, relugolix may be more effective and cause fewer cardiovascular side effects than leuprolide. By RYAN MCDONALD

A NEW DRUG THAT REGULATES the gonadotropin-releasing hormone (GnRH), resulting in the suppression of androgens (mainly testosterone), may have advantages compared with a commonly used drug of a similar type for men with advanced prostate cancer.

Relugolix sparked superior outcomes compared with leuprolide treatment in patients with advanced disease, according to data from the phase 3 HERO trial that was presented during the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program.

Advantages of relugolix include fewer cardiac side effects and no flare in testosterone levels before the drug starts to work. Relugolix is unusual among testosterone-suppressing drugs because it is the first that is administered orally, rather than being injected or implanted into muscle or under skin, said Dr. Neal Shore, medical director for the Carolina Urologic Research Center.

"The HERO trial now has established that once-daily oral relugolix … will offer patients and physicians another significant tool to consider for achieving testosterone suppression, not only because it is highly effective in achieving testosterone suppression, but (because) if patients choose to stop the medication, their testosterone recovery is much faster, so they get back to the benefits of having normal testosterone," Shore said in a recent interview with *CURE*®'s sister website, *CancerNetwork*™.

Relugolix and leuprolide reduce testosterone production to castration levels in men with prostate cancer, which deprives the disease of the fuel it needs to grow, but there are differences in how they work. Relugolix is a GnRH receptor antagonist (inhibitor) while leuprolide is an agonist (stimulator). Biologically, that difference explains why cardiovascular problems are less common with relugolix than with leuprolide, Shore said.

"The mechanism of action of an antagonist over an agonist will afford patients and physicians some comfort in knowing that there is a marked decrease in the risk of having a cardiovascular event," he said.

In the study, Shore and his colleagues enrolled 934 men with advanced prostate cancer. They received 48 weeks of either relugolix (624 patients) administered orally once a day following a one-time loading dose, or an injection of leuprolide (310 patients) every three months.

The study's main goal was to measure whether testosterone was suppressed to castration levels at 48 weeks. Additional outcomes the researchers aimed to assess included major side effects, time at which therapies were stopped, recovery of testosterone after treatment is stopped and reduction in blood levels of prostate-specific antigen (PSA), a trend that can indicate that prostate cancer is shrinking.

Shore noted that more than 90% of the patients enrolled in the HERO trial had at least one cardiovascular risk factor. Additionally, it was common for patients to have diabetes, hypertension, obesity and/or a history of tobacco use at the start of the study.

Patients who received relugolix achieved a 96.7% response rate with sustained castration through week 48, compared with 88.8% in the leuprolide group. Patients in the relugolix group (79.4%) also were more likely to log a PSA response at day 15 that was confirmed at day 29, compared with those in the leuprolide arm (19.8%).

The data demonstrated that the risk for a major cardiovascular event was reduced by 54% in patients who received relugolix. Specifically, the incidence of major cardiovascular events was 2.9% in the relugolix group versus 6.2% in the leuprolide group.

"Relugolix has the potential to become a new standard for (testosterone) suppression for patients with advanced prostate cancer," the study's authors concluded.

More than 90% of patients in both groups experienced at least one side effect. Patients in the leuprolide group (20.5%) were more likely than those in the relugolix group (18%) to experience a serious or severe side effect. While deaths were infrequent, 2.9% of patients within the leuprolide arm died versus 1.1% in the relugolix arm.

The most common side effects in either treatment arm included hot flush, or sudden onset of warmth; fatigue; constipation; diarrhea; and hypertension. Patients in the relugolix group (12.2%) were more likely to report diarrhea than those in the leuprolide arm (6.8%). However, those instances of diarrhea were not serious or severe and did not lead to treatment discontinuation. C

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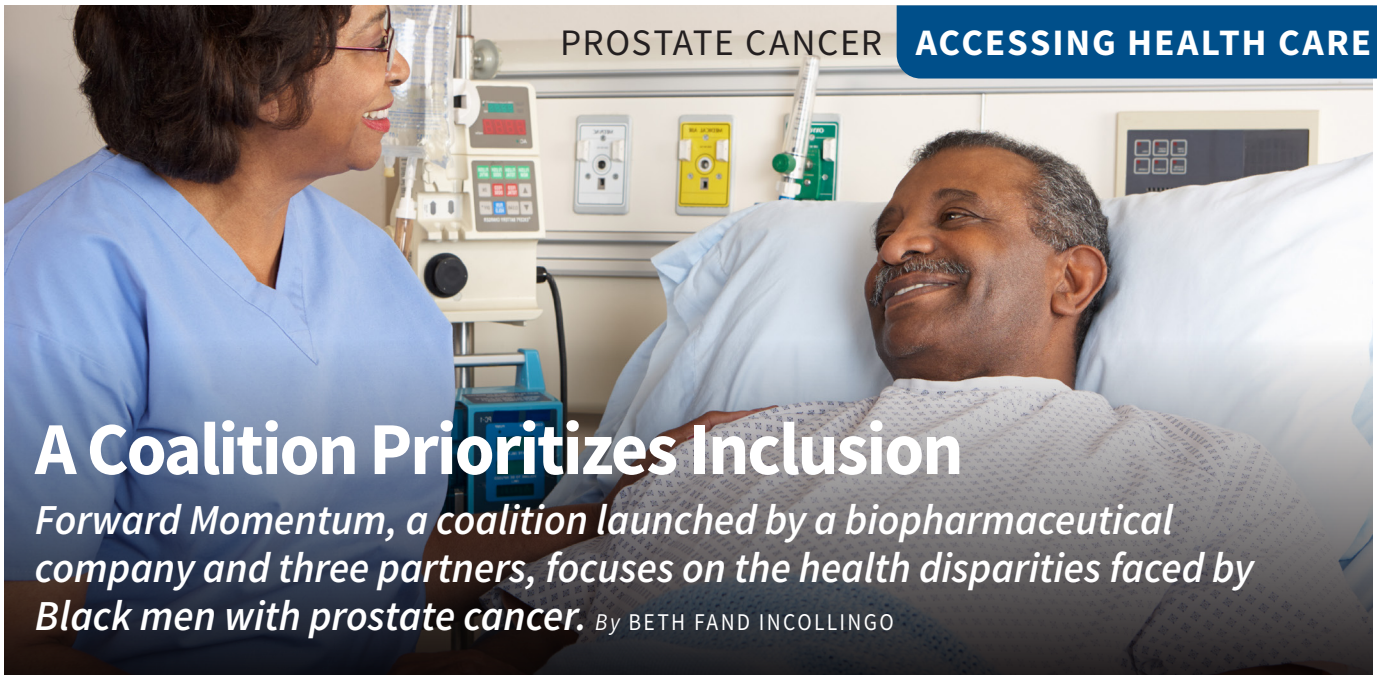


A Coalition Prioritizes Inclusion

Forward Momentum, a coalition launched by a biopharmaceutical company and three partners, focuses on the health disparities faced by Black men with prostate cancer. By BETH FAND INCOLLINGO

MANY OF THOSE WORKING in health care wish they could fix inequities in the system. Lynn Seely plans to make it happen.

As CEO of Myovant Sciences, the biopharmaceutical company developing the novel hormonal treatment relugolix for men with advanced prostate cancer, Seely knows that the disease occurs more often in Black men than it does in White men, killing them at a higher rate.

She also knows that the COVID-19 pandemic has created barriers for all men with prostate cancer because social distancing has closed many of the places they go for information and support. Compounding this problem is the fact that COVID-19 and its complications have disproportionately affected the Black community.

For those reasons, Myovant Sciences teamed up with three other organizations to form Forward Momentum, a men's health coalition with the goal of improving the lives of patients with prostate cancer.

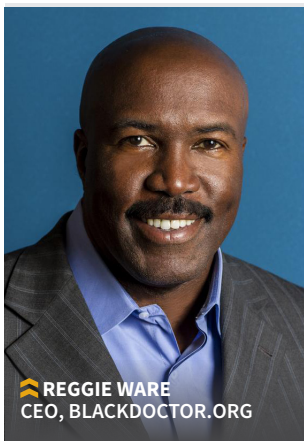
"Our men's health program is really focused on health disparities and, in particular, African American men," Seely said. "Oftentimes, they're not adequately studied, they're not adequately researched and they have worse outcomes or more aggressive prostate cancer, but a lot of that is because they don't have the same access to care and the same awareness, or they come in later for treatment. We're trying to get them much more involved in research so we get more information about them — ideally, so they get better health care."

Myovant's collaborators are BlackDoctor.org, a consumer website that shares health and wellness news with the Black community and helps readers find doctors who are likely to be culturally sensitive based on interviews or the populations they treat; patient advocacy group Movember, which is dedicated to reducing the rate of premature death among men from prostate cancer, testicular cancer and suicide; and Evidation Health, which conducts research on inventive methods of capturing, quantifying and analyzing health data.

An initial project will study the effects of the COVID-19 pandemic in a group of people representative of the racial makeup of America and the men affected by prostate cancer. The COVID-19 Experience study, conducted in collaboration with Mount Sinai's Icahn School of Medicine and the New York City Department of Health and Mental Hygiene, will measure the effects of the pandemic on men's mental health over the course of five months. BlackDoctor.org and Evidation Health also are including a focus on men with prostate cancer in the study to measure how these patients are coping with the pandemic's effects. The study's results will be shared so that the public understands how the pandemic is affecting diverse people across the United States.

Men can check their eligibility for the study, and sign up, at forwardmomentum.com.

"Representation truly matters in studies of all kinds," Christine Lemke, president and co-founder of Evidation Health, said. "It's especially critical for »



REGGIE WARE
CEO, BLACKDOCTOR.ORG

> **"Oftentimes, when there's research done across the country, there's super-low representation of our audience — Black or brown people — and so we're recruiting minorities for the study."** —REGGIE WARE

MONKEY BUSINESS / ADOBESTOCK.COM
PHOTO PROVIDED BY REGGIE WARE

diverse voices to be heard and counted given the disproportionate impact of COVID-19 on communities of color. We've designed our study to lower the barriers to participation and capture our collective lived experience of the pandemic."

Simultaneously, the coalition will work to develop digital tools that empower men to better understand and manage their prostate cancer journeys, including their mental and physical health. This will be accomplished through Movember's True North website (truenth.org/en-us), which provides information and resources to improve the quality of life and care for men with prostate cancer and their families. Improving access to accurate tools for tracking mental and physical health, such as wearables, will be part of this effort, as well as learning more about the health care-related challenges and opportunities for men during the COVID-19 pandemic.


LYNN SEELY, CEO, MYOVANT SCIENCES

"Our True North platform is designed to help men navigate their prostate cancer journey, beyond the cancer itself," said Sam Gledhill, global director of digital health at Movember. "We are committed to creating innovative tools and resources that can help men track their health and talk about their experiences with the disease, which can impact all dimensions of their lives. We are confident that through partnership we can accelerate this mission."

Those concerns dovetail with Myovant's motivation for starting the coalition.

"We are a life sciences company, but it's very important to us to actually engage with the communities that we serve to help elevate health care," Seely said. "We like to do this in what we hope are creative and new ways, and to bring together different organizations that approach problems from very different perspectives to make a major impact in health care. It's so important to us because there are many who are getting left behind and don't have access to care."

The ultimate goal is "to educate the patient and get him back in the center of the conversation," she said, "so that he is comfortable talking about these problems and getting the help from a health care provider that he needs."

UNDERTAKING A CHALLENGE

But when dealing with an underserved group of patients, securing participation can be easier said than done, and it will be up to BlackDoctor.org to pave the way. CEO Reggie Ware is thinking about how to meet that challenge as his organization takes on the task of recruiting patients for the COVID-19 Experience study.

"The patient journey is different for our audience," Ware said. "The biggest difference is the question of: 'Can we trust the doctor, or not?' The other piece that's really big is that we did a study on our site, and it showed that only 10% of our audience feel that they will be treated fairly in the health care system. If a person doesn't feel that they're going to get a positive outcome, they're less likely to go to the doctor."

Distrust of the health system among Black patients dates in part back to the 1932-1972 study of untreated syphilis in black men, conducted by the U.S. Public Health Service and the Tuskegee Institute, Ware said. Participating men were not given the opportunity to provide informed consent or given adequate treatment to cure their illness, even when penicillin became the standard of care in 1947, according to the Centers for Disease Control and Prevention.

"I've never run into a Black person who didn't know about the Tuskegee experiment," Ware said.

That has had a chilling effect on Black participation in clinical trials, he said, and is something Forward Momentum is committed to overcoming as it recruits men to be part of its study.

"Oftentimes, when there's research done across the country, there's super-low representation of our audience — Black or brown people — and so we're recruiting minorities for the study," Ware said. "This is going to be one of the first times in the country's history that there's a group of patients in a study who are representative of what this country looks like."

Seely said she has high hopes that Black patients will participate, because the study will seek information rather than offering medical care. She expects the project to be a good way to create comfort with the trial process.

Along the way, researchers are likely to learn that members of the Black community have had some concerns in common during the COVID-19 pandemic, Ware said.

Relatively few Black people have jobs that allow them to work from home, he said, "so our message isn't 'Work from home,' but 'How do you stay safe when you still have to go to work every day?'"

He added that, based on recent research by BlackDoctor.org, 50% of the organization's audience members expect to refuse a COVID-19 vaccine, while another 20% will have serious reservations about being vaccinated. "We're brainstorming ways to turn that around," he said.

Ware praised Myovant and Seely for putting the coalition together. "They understand that if you bring people to the table and you have meaningful conversations, then it's going to go well," he said, "and people are going to look at you differently than the rest of the market, which pretty much just takes your existence for granted. They're a beacon of light in an industry that I think could use some light."

He added that, "Once we get everybody to take the vaccine, I think that there are going to be some pretty powerful changes and opportunities for us to come together and really work on health equity and health disparities and really afford some meaningful partnership. I'm hoping that this becomes the first of many partnerships that are going to help people manage their lives."

PHOTO PROVIDED BY LYNN SEELY

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KANSAS STATE POLYTECHNIC

Student pilot **BRANDON STEVENS**, after receiving treatment for testicular cancer, is using his wings to give back to his community. Here, he helps on a mission for Pilots N Paws.

Paying It Forward

After enjoying visits from therapy dogs during treatment for testicular cancer, a student pilot decides to volunteer to transport pets needing rescue, shelter or adoption. By BETH FAND INCOLLINGO

WHEN BRANDON STEVENS looks back at his treatment for testicular cancer, he remembers the bright spots in that dark time. With support from his family, friends and hospital volunteers, he was able to stay positive — especially when he was visited by the four-legged members of his care team.

"They had a lot of therapy dogs, mostly labs and golden retrievers. Just seeing a dog in the hospital when you're going through these treatments cheers you up a lot," recalls Stevens, who, after receiving his diagnosis shortly after graduating high school, underwent surgery and then chemotherapy in the fall of 2015. He was treated at the UCHealth Cancer Care and Hematology Clinic in Greeley, Colorado.

The next year, grateful to be in remission and studying to become a pilot, Stevens felt inspired to help others in need, just as his supporters had helped him. Remembering the therapy dogs, he started volunteering for Pilots N Paws, a nonprofit organization that transports pets to facilitate their rescue, shelter or adoption. Stevens has earned his private pilot's license at Kansas State University Polytechnic Campus in Salina, where he is a senior expecting to graduate in the spring with a bachelor of science in aeronautical technology and a minor in aviation safety; he participates in the volunteer program on weekends. In fact, he uses his own money to rent planes and fuel them up for the trips, the school has reported.

"Everyone has done so much for me, and I had a lot of exposure to good people who were going out of their way and not being paid to help me, so it's natural to want to do that. I can't think of a better way to do it than to give back to the community," he said. "I can't imagine living and not (making) some type of contribution to something larger than myself."

It only took one mission to get Stevens hooked on delivering dogs. "It was through a Husky rescue mission that was sending the dog to a new owner," he said. "We

PHOTO PROVIDED BY BRANDON STEVENS

STEVENS, who devotes a lot of his free time to helping animals in need, spends a moment with a dog.

delivered it to a family, and to see the kids’ eyes light up as they saw the dog — that’s what really sealed the deal for me.”

Stevens feels connected to the organization not only because he has owned dogs, but because he hasn’t forgotten how much the hospital’s therapy dogs helped him through his treatments, especially chemotherapy, which he found both terrifying and draining. “The sheer amount of chemicals that were being put in was overwhelming and scary,” Stevens said. “There’s a lot of uncertainty, because you don’t know how you’re going to react or exactly how it’s going to feel.” With chemotherapy scheduled every other week, it turned out that he alternately felt fine — and then terrible.

What most surprised Stevens was the mental fog, or “chemo brain,” that he experienced during treatment. “I would be out with my family and I couldn’t really comprehend what was going on around me,” he said. “I just wasn’t there mentally. … I thought something was wrong with me for a while, because I couldn’t remember some things, and my brain was just a little slower than I remembered it being.”

Although the problem has lingered, he said it has “gotten better over the years with practice and constantly challenging with puzzles. One of my biggest regrets was not going through more academic exercises while I was going through chemotherapy.”

As a college student in the professional pilot program who studies every day and is striving to earn his aviation ratings, “I have to work longer, because it takes longer for the information to stick,” he said. “I require a little more studying than had I not had cancer. It’s really just persistence and constantly sticking through it.”

Still, it’s important to him to find the time to volunteer. In addition to his work for Pilots N Paws, Stevens and some friends are working to create an aviation-related organization to help children who have cancer.

“The big thing for me when I was going through treatment was having something afterwards to look forward to, seeing the light at the end of the tunnel,” he said. “One way we could help do that is by introducing kids to aviation and visiting kids who are going through really similar situations and talking with them. We really want to start scheduling visits and then eventually working up to introductory flights to get kids’ minds off what’s going on and open up a little bit of happiness there.”

For Stevens, connecting aviation and volunteerism gives meaning to both.

“A lot of times you work so hard on getting a rating (a certification allowing a student to fly a certain type of aircraft) and you start to feel a little selfish,” he said. “You think ‘Why am I doing this?’ I don’t know if I would have had that mindset before I had cancer, but I think a lot of cancer survivors are the same way and want to give back.” C

Finding New Value in an Old Standard

For some patients with metastatic kidney cancer, undergoing surgery after targeted or immune therapy sparks better health outcomes. By BRITTANY COTE AND BETH FAND INCOLLINGO

PATIENTS WITH METASTATIC renal cell carcinoma (RCC) who were initially treated with targeted drugs or immunotherapies had better outcomes if they later underwent surgical removal of the kidney tumor, an analysis has found.

Cytoreductive nephrectomy is a surgery designed to remove all cancerous cells from the kidney and any involved surrounding organs, such as the spleen, pancreas, intestines or liver. Adding it to treatment extended the length of life for patients in the study, according to Dr. Ziad Bakouny, a postdoctoral genitourinary oncology research fellow at Dana-Farber Cancer Institute in Boston.

That finding should resolve an ongoing controversy about the value of cytoreductive nephrectomy at a time when targeted drugs and immunotherapies are taking center stage in the treatment of stage 4 kidney cancer, Bakouny said in an interview with *OncLive*®, a sister publication of *CURE*®.

"With the present database of this very large, retrospective study," Bakouny explained, "there is currently no evidence to say that cytoreductive nephrectomy no longer has a place in the immune checkpoint inhibitor era, despite the fact that (immunotherapies) are effective."

EXTENDING SURVIVAL

The study included 4,639 patients who received initial diagnoses of metastatic RCC and were treated with either checkpoint-inhibitor immunotherapy or targeted therapy between 2009 and 2019. A total of 4,202 of the patients received a targeted therapy, and 2,631 from that group underwent cytoreductive nephrectomy while 1,571 did not.

Meanwhile, 437 of the patients received treatment with immune checkpoint inhibitors, 245 of whom followed that with cytoreductive nephrectomy while 192 did not.

The analysis was retrospective, looking back at the patients' cases after treatment had occurred. The data were gathered from the International Metastatic RCC Database Consortium (IMDC), which includes patients from more than 40 centers across the world.

At a median follow-up of 38.5 months, those in the targeted therapy group who received cytoreductive nephrectomy experienced a median overall survival (OS) of 26.5 months versus 10.3 months in those who did not undergo cytoreductive nephrectomy. Those in the immune checkpoint inhibitor cohort with and without a cytoreductive nephrectomy experienced a median OS of 53.6 months versus 21.4 months, respectively.

TESTING THE VALUE OF SURGERY

The researchers embarked on the study because the advent of targeted drugs and immunotherapies has raised questions about whether cytoreductive nephrectomy – which in the past was routine for patients with RCC diagnosed in the metastatic stage – is still necessary, Bakouny said.

Before 2005, the surgery was a standard strategy because there were very few systemic therapies that could be considered as alternatives, Bakouny noted. But after that year, the targeted drugs Sutent (sunitinib) and Nexavar (sorafenib) were found to improve the survival of patients with this disease.

"As more effective systemic therapies (emerged), the question became: 'Is cytoreductive nephrectomy still relevant?'" he said.

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PHOTO COURTESY OF DANA-FARBER CANCER INSTITUTE

> **"With the present database of this very large, retrospective study, there is currently no evidence to say that cytoreductive nephrectomy no longer has a place in the immune checkpoint inhibitor era, despite the fact that (immunotherapies) are effective."**
>
> *— DR. ZIAD BAKOUNY, Dana-Farber Cancer Institute*

Large studies have generated different answers to that question.

While some retrospective studies established that the surgery was still effective in the era of targeted therapies, a recent, large clinical trial called CARMENA, which treated patients with Sutent either by itself or after cytoreductive nephrectomy, showed that the drug alone did not lead to worse outcomes. Bakouny pointed out that this outcome could be related to the fact that the trial included patients with higher-risk RCC. On the other hand, his own analysis focused on patients who were younger and had lower-risk disease, although their cancers had some characteristics that indicated aggressiveness.

Armed with evidence that surgery had value in the age of targeted drugs, Bakouny and his colleagues set out to determine whether it was also effective in patients who received immunotherapy.

The investigators used two styles of analysis designed to correct for factors that could skew results. A multivariable analysis controlled for the effects of factors including age and IMDC risk group, and a propensity-based analysis balanced out bias in the selection of study participants.

"We found that the same signal we had seen in the targeted therapy era, we saw again in the immune checkpoint inhibitor era," Bakouny said.

APPLYING THE FINDINGS

Still, that doesn't mean that every patient with metastatic RCC will benefit from cytoreductive nephrectomy given in conjunction with targeted treatment or immunotherapy. According to Bakouny, the CARMENA trial found that patients who had one IMDC risk factor (such as low hemoglobin or high calcium levels) benefited from surgery before receiving Sutent, especially if they had only one site of disease spread, while those with two risk factors did not.

"We see the same signal in our data, as well," Bakouny said. "As we see effective systemic therapies emerge, we're going to (increasingly use cytoreductive nephrectomy in) more selected populations."

In fact, he said, that's already happening in medical practices throughout the world, which are selecting patients with the lowest-risk disease to receive regimens that include both surgery and either a targeted or immune-stimulating drug.

Bakouny said it makes sense that these patients would be most likely to benefit.

"Although factors like normal hemoglobin and normal calcium have been shown to correlate with good prognosis in patients in general," he said, "these are patients who would not progress and would be perfect for a cytoreductive nephrectomy, at least until we have other evidence to suggest otherwise."

LOOKING AHEAD

Clinical trials that are in progress will help confirm whether such combination regimens should continue and in which patients, Bakouny said.

The PROBE trial, as well as a separate trial in Europe, is looking at initial treatment with the immunotherapies Opdivo (nivolumab) and Yervoy (ipilimumab) followed by cytoreductive nephrectomy. Meanwhile, the CYTOSHRINK trial is testing initial Opdivo/Yervoy followed not by surgery, but by stereotactic body radiation therapy (SBRT). "Although this is not cytoreductive nephrectomy, the primary lesion is being targeted with SBRT, so it is a similar concept," Bakouny said.

Many of these trials are looking at deferred surgery, rather than initial surgery followed by drugs. "As such, many of these trials are now looking at very effective regimens, such as (giving Opdivo/Yervoy) or other immune checkpoint inhibitor-based regimens, getting a deep partial response and then just removing the remaining bulky mass and trying to render the patient (to have no evidence of disease), which makes a lot of sense," Bakouny said. C

COVID-19: A Catalyst for Better Care?

A woman living with metastatic kidney cancer considers how changes in caring for patients with renal cell carcinoma during the pandemic may actually lead to better practices. By DEB MASKENS

DURING THE CHALLENGES WE face due to the COVID-19 pandemic, I've been searching for any positives that might come out of this for patients with kidney cancer, also known as renal cell carcinoma (RCC). Here are four that I've come up with:

1. We may learn that fewer doses of immunotherapy are just as effective as the number of doses originally tested and approved. For years, we've heard whispers in the hallways that we may not need as much drug. Maybe, just maybe, we will look back on 2020 real-world patient outcomes and learn that we can safely space out those infusions and give patients a treatment break, perhaps making plans to resume it later — and in select patients, finding that we can stop the therapy indefinitely. That could lead to fewer immune-related side effects — and, of course, lower costs for our health care system and for patients.
2. The global pandemic could be the impetus needed to stop surgeons from operating on the smallest renal tumors visible on imaging without further investigation. We know that 20% of these small tumors are noncancerous, and many will never develop metastasis. So, possibly, the data coming out of 2020 will prove that the rush to surgery for renal tumors under 4 centimeters can instead be replaced with a fulsome discussion of if and when to operate after some months or even longer, as this is not a medical emergency.
3. Around the world, we are seeing some practical changes in how kidney cancer drugs are being sequenced — and, in many countries, we will be collecting patient outcomes that will inform us all. Initial therapy for stage 4 kidney cancer often includes infused immunotherapy, but during the pandemic, that has changed to reduce COVID-19 risk for some patients from travel to the physician's office or hospitalization from potentially serious complications. A patient whose disease is deemed to be at favorable risk according to International Metastatic RCC Database Consortium (IMDC) standards might instead continue with active surveillance or start with a targeted treatment known as a tyrosine kinase inhibitor (TKI), which can be taken orally at home, with a plan to use immunotherapy afterward. Meanwhile, patients with intermediate- or poor-risk disease according to IMDC standards will likely start with an immunotherapy such as Keytruda (pembrolizumab) given with the TKI Inlyta (axitinib). This regimen could pose less risk of the type of severe immune-related toxicities that may require hospitalization than two immunotherapies, Yervoy (ipilimumab) and Opdivo (nivolumab) given together. We can all expect to learn from these changes in sequencing.
4. We may also discover that many patients, under certain circumstances, can stretch out their timeline of imaging recommendations to reduce the number of scans they receive. A lot of us can safely push out our scans a month or two without too much risk — for instance, imaging every six months instead of every four months. In the long-term surveillance or metastatic setting, is the associated risk/benefit trade-off reasonable? I guess we'll learn!

DEB MASKENS is a patient living with metastatic kidney cancer. She is a member of the Kidney Cancer Association's Patient & Caregiver Advisory Council and serves as a patient advocate on the National Cancer Institute's Renal Task Force.

Many clinical trials have been suspended, and this will undoubtedly slow progress. However, the practical changes in RCC care due to the COVID-19 pandemic bring many potential positives which could possibly become new standards of care. Do you see others?

PHOTO COURTESY OF KIDNEY CANCER ASSOCIATION

How To Be a Sensitive Caregiver

A survivor has seven etiquette tips for friends and loved ones of people with cancer. By RON COOPER

I HAVE STAGE 3 prostate cancer and I own it. Now, bug off! See what just happened? For cancer survivors like me, "cranky" might be a gross understatement. You, as a caregiver, may want to be part of my cancer journey while being careful to avoid stepping on any land mines along the way. Who can blame you?

Let's suppose you're itching to tell me about natural treatments. Nope, don't go there. I'm just getting used to my cancer specialists and their advice. Or you may want to recount the story of your uncle who died a terrible death in the throes of cancer, noting that you're sure I won't end up like that. Nope, nope and nope! Never compare someone else's cancer with mine. The shoe never fits.

To empathize and soothe someone with cancer:

1. **Talk about anything but cancer.** Cancer does not define us survivors. Yes, sometimes it leaves us exhausted and frustrated. Sometimes we can't even enjoy a silly sitcom. (Sorry, "Seinfeld.") Still, we're as well-rounded as the next person. Cancer talk 24/7? Heck, no! Talk weather, sports, news or anything but cancer.

2. **Talk about cancer.** Wait — you're probably thinking that I just said to talk about anything but cancer. Here's the thing: Survivors do want to talk about the "Big C," but on our own terms and at our own pace. Be there to empathize and soothe.

3. **Show affection.** A hug is deeply felt during the cancer journey. I would give a million bucks for a hug, but not a dime for your Googled research. A warm smile is remarkable, spectacular and memorable. These are precious gifts for the person living with cancer. By the way, what I said about hugs back there? Make them virtual until this crazy pandemic dies off.

4. **Give the right gifts.** Gifting is appreciated. Well, most of the time. Soup is always good. It warms the body and the beleaguered soul. Pastry? Check. Artisan bread? Check. But I know what you're thinking: "Should I bring a 'F**K Cancer' T-shirt or coffee mug?" You know your loved one best. The diagnosis may be so fresh and painful that cancer swag would be a little premature. Timing is everything. Please leave your deliveries at the doorstep. You'll get a nice thank-you card.

5. **Don't make bad suggestions.** Some people may say, "Journaling might help you." Early on, I'd be thinking, "Why in the world do I want to pour out my heart and soul on paper when the words 'I am going to die!' roll around in my head all day? I'm trying with all my might to unthink this crazy disease, only to find it around every bend in the road."

6. **Make good suggestions.** You might say, "Journaling might help you." Yes, I'm contradicting myself again. Well, here's the skinny: Journaling may be the very best outlet when I'm ready to write. Thankfully, I've been in remission for four years. To give back to those helping me along my journey, I wrote a book to lift survivors and caregivers, and I blog on my author website. So, yes, journaling is part of my world. But, please don't thrust a journal into the survivor's hands until they're ready to write.

7. **Don't go by the numbers.** You've been Googling, haven't you? I can see that printout in your top pocket. Please stay away from reciting numbers on the prognosis for anyone's cancer. You know, 20% chance of survival for the first five years. Fifty percent for the next five. I may be still processing everything, factoring in how treatment will improve my quality of life. Now you come along with a bagful of stats. Shoo! Ever the eternal optimist, you may want to say, "Well, there are always experimental treatments. I read a report from MD Anderson, blah, blah, blah …." Sorry, I had to cut you off there. I know you want to help, but please hold onto your printout.

There you have it: etiquette to embrace or ignore at your own risk. Now, get out there and travel the cancer journey with your survivor. Just zip that lip and don't go overboard, and virtual hug your way into the history books. Good luck to all of us. We're going to need it!

***Ron Cooper** turned to freelance writing and book editing after a 25-year career as a newspaper reporter. At Gilda's Club, which keeps him grounded, he is active in a support group and a writers' group. Cooper is the author of three books, the latest of which is about his cancer journey: "A Grateful Survivor: Tips and Tributes for Cancer Caregivers" (Amazon). He is passionate about improving communication between the caregiver and the cared-for. Ron blogs on cancer, the coronavirus and other topics at* **RonCooperAuthor.com.**

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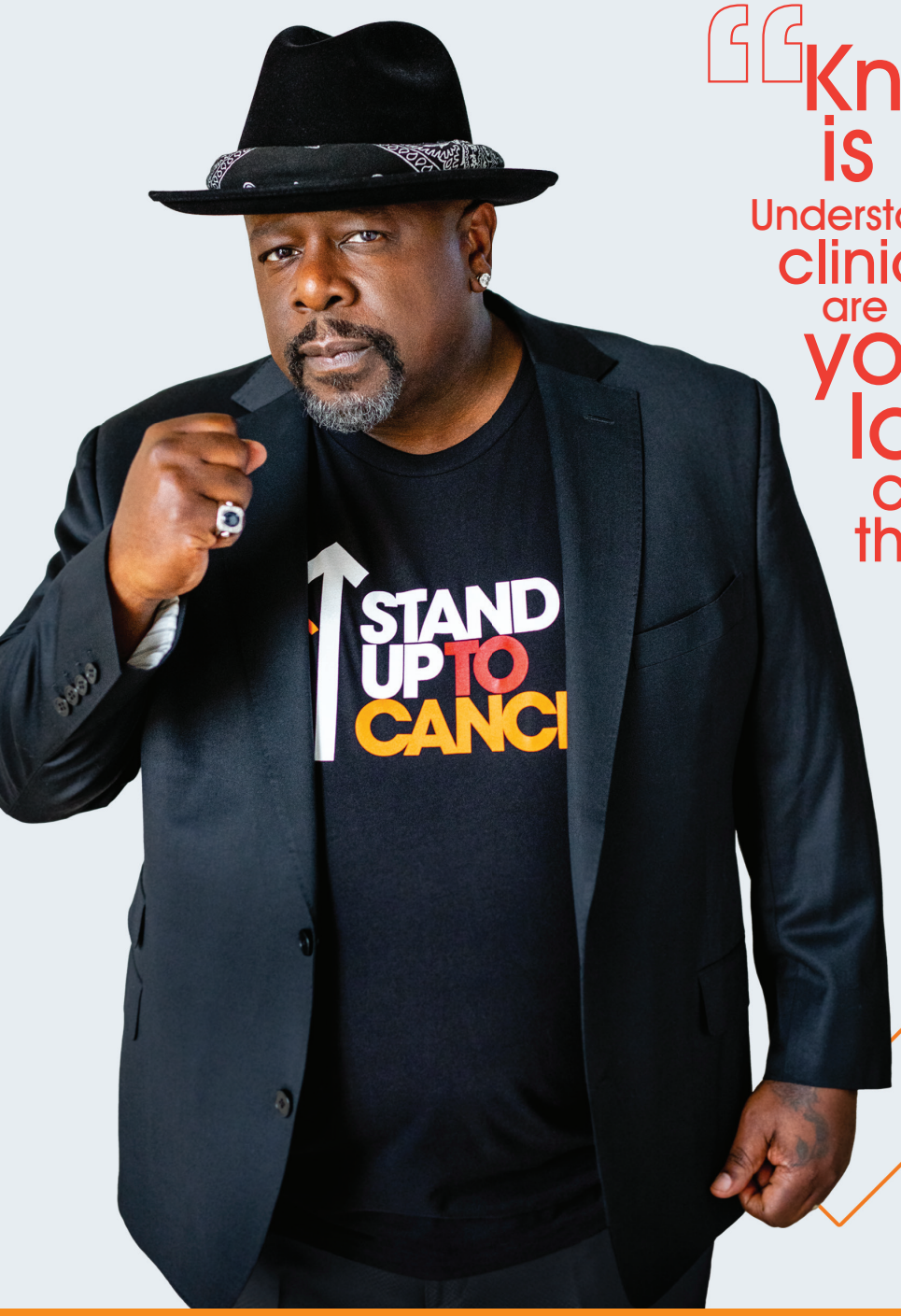

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