Many Men with Metastatic Prostate Cancer Are Not Getting the Recommended Treatments

Individuals may have to advocate for themselves to get the highest quality care.

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Since 2017, recommendations for the treatment of metastatic prostate cancer that can be controlled by shutting off its supply of hormones, often called hormone- or castration-sensitive prostate cancer, have shifted radically.

Giving a single drug to suppress testosterone production—for years, the standard of care—is no longer considered enough. Guidelines in the United States now recommend giving a combination of two different drugs to block hormones in two different ways. For people at the highest risk of their cancer getting worse, guidelines recommend adding chemotherapy as well. In clinical trials, both approaches have shown that they help people live longer.

However, results from a new study indicate that these guidelines have largely not trickled down into practice. In a survey of U.S. doctors who care for patients with prostate cancer, almost 70% reported not using this combination therapy up front for patients with hormone-sensitive metastatic prostate cancer.

The findings, published December 9 in JAMA Network Open, are very concerning, said the study's lead investigator, Neeraj Agarwal, M.D., of the University of Utah's Huntsman Cancer Institute.

"In the United States, the majority of patients aren't receiving life-prolonging [combination therapies], despite the fact that [clinical] trials have shown that they lead to a really meaningful improvement in overall survival," Dr. Agarwal said.

In their survey responses, almost 60% doctors who did not prescribe combination treatments for most of their patients expressed concerns that giving more than one drug at a time would have too many side effects. However, in clinical trials, researchers actually saw the opposite effect: People who received the recommended combination treatments reported having a higher quality of life overall than those who got only a single drug.

The improved quality of life may reflect the ability of the combination treatment to better reduce symptoms, such as the pain and fractures caused by the spread of prostate cancer to the bones,

explained NCI's Fatima Karzai, M.D., who studies new treatments for prostate cancer but was not involved in the study.

"When somebody has a lot of disease [in their body], and they have symptoms from the disease, if you put these drugs together, people actually feel better, because their symptoms get better sooner," Dr. Karzai said.

Many doctors also weren't up to date on the current guidelines, reporting that they thought use of a single drug remained the standard of care.

"One drug alone is no longer sufficient" for these patients, said Dr. Agarwal. "Combining two [or more] really improves survival without compromising quality of life. But, if you look at the implementation of these data in the real world, we see a real disconnect."

Some of the guidelines in question were only updated within the past 2 years, explained Gurvaneet Randhawa, M.D., M.P.H., of NCI's Healthcare Delivery Research Program, who was not involved with the study. This may not be enough time for new knowledge to spread widely among physicians.

However, Dr. Randhawa added, it highlights the need for research into understanding how best to provide the information from the latest guidelines to clinicians. "There are likely differences in the [best] ways to integrate the guidelines into the workflow and decision support for providers in different specialties," he said.

A one-two-three hit

In men with metastatic hormone-sensitive prostate cancer, intensified treatment with the recommended drug combinations delivers a one-two hit to hormone-sensitive cancer cells.

The first hit, standard androgen deprivation therapy with drugs like goserelin and leuprolide, suppresses the production of testosterone by the testes. The second hit is a newer class of drugs, called androgen receptor pathway inhibitors (ARPIs). These drugs—which include abiraterone, apalutamide (Erleada), darolutamide (Nubeqa), and enzalutamide (Xtandi)—stop cancer cells from using any testosterone that remains in the body.

And for people with the most aggressive disease, a third hit, chemotherapy (specifically a drug called docetaxel) can directly kill prostate cancer cells.

Previous studies from Dr. Agarwal's team and others have found that, despite clinical trials demonstrating the superiority of more intensified treatment with combination therapies in clinical trials, these findings were largely not changing real-world practice.

"So we wanted to delve into why," he said. "What are the reasons for this?"

The researchers used data collected between July 2018 and January 2022 by the Adelphi Real World retrospective survey, which regularly asks representative samples of doctors across the country detailed questions about the treatments they prescribe for their patients and why they chose those treatments. The survey also links doctors with their respective patients' medical records, to let the researchers verify the treatments received.

The survey collected answers from 107 doctors and covered the treatment of 617 people with metastatic hormone-sensitive prostate cancer over the three-and-a-half-year window of the study. Doctors included medical oncologists and urologists from both community hospitals and academic cancer centers.

Overall, only about 30% of patients got the recommended intensified treatment. The reasons given for not prescribing intensified treatment were usually not based on up-to-date data. For example, for about 19% of patients who didn't receive intensified treatment, doctors reported that a single drug was more effective. For another 31% of patients, doctors stated that clinical trials hadn't shown improved survival with treatment intensification.

Doctors who reported more aggressive goals for lowering PSA levels, in hopes of eradicating as much prostate cancer as possible, were more likely to prescribe the recommended drug combinations.

Other factors didn't seem to make much of a difference. For example, concerns about insurance coverage were rarely cited as a reason for not prescribing combination therapy.

Doctors: Don't save combination therapy for later

Dr. Agarwal suggested one potential reason for why some clinicians still use single-drug androgen deprivation therapy for patients with hormone-sensitive disease. In most people with metastatic hormone-sensitive prostate cancer, the cancer eventually changes so that it can grow without being reliant on testosterone from the testes, known as hormone-resistant (or castration-resistant) disease.

Hormone-resistant disease is harder to control, with only about 30% of people with this form of prostate cancer surviving more than 5 years.

However, many of the same drugs are used to treat hormone-sensitive and hormone-resistant disease. So, providers may be thinking that if they use the more intensified treatment for patients with hormone-sensitive disease, he said, "'What will [I] have left for future use when the disease progresses?'" In other words, they want to keep some of these therapies in reserve "for when castration resistance happens."

And in the study, he noted, about 16% of men who initially got single-drug androgen deprivation therapy went on to get more intensified treatment when they developed hormone-resistant disease. Other recent studies have also found that reserving treatment intensification for this

scenario is one of several common reasons for not using it in patients with hormone-sensitive disease.

Nevertheless, Dr. Agarwal added, “that’s not the right way to treat patients.” Multiple clinical trials have shown that people who receive combination therapy when their disease is still hormone sensitive live longer than those who get it later, after their disease becomes hormone resistant.

“So the message here is: Don’t wait for disease progression,” he said. But that message needs to be spread much farther and wider than it has to date, he added.

Patients: Understand your disease

For now, explained Dr. Karzai, patients who have a new diagnosis of metastatic hormone-sensitive prostate cancer may have to advocate for themselves to get the highest quality care.

“I’m not suggesting that patients read all these clinical trial data and try to figure them out on their own,” she said. “But really understand your disease. If it’s hormone-sensitive, talk to your doctor about what that means, and how the amount of cancer in your body affects your treatment choices. Talk about side effects. Ask about two- and three-treatment combinations and how they will make you feel. Ask: ’What are the benefits? What are the risks?’”

It can help to have a family member or another trusted person help you take notes and ask questions, Dr. Karzai continued. “A lot of times, to be a patient by [yourself] in a room with a doctor, it’s just too much information [to take in]. And I also highly recommend getting a second opinion,” she said.

In the longer run, said Dr. Agarwal, “we need to get the evidence for combination treatment to our colleagues … in a simple format that’s time-efficient for them to use.”

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