Watchful Waiting Beats Androgen Deprivation Therapy in Early Prostate Cancer

By Vicki Brower

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ometimes not treating a patient with cancer may be the best treatment—at least for early prostate cancer, a new study indicates. A retrospective analysis of nearly 20,000 men aged 66 years and older showed that men without aggressive disease who took the “watchful waiting” approach did as well as or better than those who took androgen deprivation therapy (ADT).

ADT is most often used as a palliative treatment for advanced prostate cancer or in patients with early disease who are at high risk of progression. Its routine use in other early-stage patients is frequent but controversial. Commonly prescribed ADT drugs include the gonadotropin-releasing hormone agonists, such as leuprolide and buserelin, and anti-androgens such as flutamide and nilutamide.

In the recent study, Grace Lu-Yao, Ph.D., of the University of Medicine and Dentistry of New Jersey, and colleagues looked at survival rates in more than 19,000 men on Medicare who had not received any therapy for stage T1 or T2 prostate cancer. They found that men who received primary ADT as their first-line treatment had lower 10-year disease-specific survival than those who took no drugs but similar 10-year overall survival. The only exceptions were patients with poorly differentiated cancer, which carries a higher risk. This group had better prostate cancer-specific survival with ADT—but not better overall survival—than those not receiving therapy. The results, published in the *Journal of the American Medical Association* in July, add to the growing evidence that ADT does not benefit most men with early prostate cancer.

“Our study is a response to the growing practice of offering treatment to men with local disease, rather than watchful waiting,” said one of the authors, Peter Albertsen, M.D., professor of surgery at the University of Connecticut in Farmington. “While it may make intuitive sense to treat patients, and doctors make money doing so, the early use versus delayed use of these drugs does not work and is not a rational response,” Albertsen said. “We are grossly overtreating men with early-stage prostate cancer.”

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**Who Benefits?**

Urs Studer, M.D., professor and chair of the department of urology at Switzerland’s University of Bern, who did not take part in this study, agreed that patients with a low risk of dying from the disease should not be treated. “Patients who have a small volume of cancer, whose prostate-specific antigen, or PSA, level rises slowly, and who have a low Gleason score [which indicates whether a tumor is well differentiated and low risk], have a very small risk of dying of the disease,” Studer said. “These are the patients who should not receive ADT.” Conversely, men whose Gleason score is 8 or higher, and whose PSA doubles in less than 12 months, are at higher risk of dying of prostate cancer within 3–5 years and should receive ADT, he said.

One of the issues in treating early prostate cancer is determining who is at high risk. Studer conducted a randomized controlled study in nearly 1,000 patients with early-stage disease that was not suitable for localized curative treatment. The men received ADT either immediately at diagnosis or when their tumors began to grow. The results, published in the *Journal of Clinical Oncology* in 2006, showed that for these patients, immediate treatment resulted in a modest, statistically significant difference in overall survival but no difference in disease-specific mortality or overall symptom-free survival.

An update of that research further refined who benefits most from ADT and when the treatment should be given. Studer examined patients’ baseline PSA levels, PSA doubling times, and risk of death, and he found that patients with a PSA greater than 50 ng/mL or a PSA doubling time of less than 12 months were at increased risk of dying from the disease and might benefit from immediate ADT. Patients with a baseline PSA less than 50 ng/mL or a slow PSA doubling time (>12 months) were more likely to die of causes other than prostate cancer. “Those patients could be spared the burden of immediate ADT,” he said.

Basic research in prostate cancer–prone mice supports these and similar findings. Last year, Cory Abate-Shen, Ph.D., professor of urology and pathology at Columbia University, demonstrated that chronically reducing androgen levels in genetically mutated mice prone to prostate cancer actually fueled disease growth compared with mice whose androgen levels were maintained in the reference range. Abate-Shen had expected that lower levels of androgen would reduce tumorigenesis, not fuel it.

**ADT Use Prevalent**

Despite the evidence that prescribing ADT to patients with very early disease is
not effective, its use has risen over the past two decades. Vahak Shahinian, M.D., assistant professor of medicine at the University of Michigan, estimates that with more than 200,000 new cases of prostate cancer diagnosed annually in the U.S., about 80,000 receive ADT within 6 months of diagnosis.

Shahinian reported in 2005 that the use of gonadotropin-releasing hormone agonists to treat localized prostate cancer increased consistently between 1991 and 1999 for all ages, stages, and grades of prostate cancer. And for men aged 80 years or older with localized prostate cancer and low- to moderate-grade disease, the use of ADT grew from 3.7% in 1991 to 30.9% in 1999.

Another study, by Matthew Cooperberg, M.D., of the University of California in San Francisco, documented the growing use of primary ADT and neoadjuvant ADT, showing that the use of primary ADT rose sharply between 1989 and 2001, from 4.6% to 14.2%, from 8.9% to 19.7%, and from 32.8% to 48.2% in low-, intermediate-, and high-risk groups, respectively (J Natl Cancer Inst 2003;95:981–9). Neoadjuvant use also increased in conjunction with radical prostatectomy and external-beam radiotherapy.

Michael Barry, M.D., of Massachusetts General Hospital reported in 2006 that the use of ADT in older American men rose from 1.8% to 2.9% between 1993 and 2000. He found that this rise was associated with early detection and more aggressive treatment, i.e., more PSA testing, more prostate biopsies, and more radical prostatectomies.

The other downsides of ADT include its cost and serious side effects. It is an expensive drug, Shahinian said, although costs have come down since they peaked in 2003. At that time, ADT accounted for the second-highest Medicare Part B expenditure at about $1.2 billion. Since then, he said, there has been a dramatic reduction in cost of more than 50%, due primarily to the changes in Medicare reimbursement for gonadotropin-releasing hormone agonists that took place in 2004 and 2005.

The side effects seen with ADT can be serious. In addition to impotence, toxic effects include osteoporosis, metabolic syndrome, diabetes, cardiovascular disease, muscle loss and fat gain, insulin resistance, and increased risk of bone fractures.

ADT drugs can also have major negative effects on quality of life. Arnold Potosky, Ph.D., of Georgetown University and colleagues reported in 2002 that 80% of men with early prostate cancer who were treated with ADT said that they had become impotent, compared with 30% of untreated men (J Natl Cancer Inst 2002;94:430–7). Men in this study who received ADT were also five times more likely to report breast swelling and hot flashes. Moreover, men treated with ADT reported a reduction in physical comfort and vitality 1 year after therapy.

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In another study, published in 2001 in the Journal of Clinical Oncology, that compared ADT drug treatment with orchiectomy (surgical castration), patients taking ADT had more breast swelling and physical discomfort, poorer self-assessed overall health, and less energy. And in September 2008, scientists at New York City’s Memorial Sloan-Kettering Cancer Center reported in the journal Cancer that ADT patients experienced a 47%–69% decline in at least one cognitive area, often on spatial and multitasking abilities, as well as declines in memory and concentration.

The estrogen patch, which is in early-stage testing as an alternative to other ADT drugs, may carry fewer side effects, according to a recent study published online in August in BJU International.

Reasons for Overuse

Why ADT use continues to rise in early prostate cancer is a topic of debate. James Talcott, M.D., director of the center for outcomes research at Massachusetts General Hospital Cancer Center, assessed the overuse phenomenon harshly, laying responsibility at the feet of physicians.

“High or low use of [primary ADT] is a marker of inappropriate care, of physicians’ overly aggressive practice styles, that separates physicians into [those who are] more or less willing to use a cancer treatment without evidence justifying its use,” he said.

“Patients find drug treatment more attractive than orchiectomy because it is less immediately devastating to male identity, and there are also financial incentives for doctors to give the drugs,” Talcott added. “These drugs are a cash cow for some physicians.”

There is some evidence supporting this view. Using the SEER (Surveillance, Epidemiology, and End Results)–Medicare linked database, Shahinian found that the strongest determining factor for ADT use was the treating physician, concluding that “which urologist a patient sees may be more important in determining whether [the patient] will receive ADT than tumor or patient characteristics.” (J Natl Cancer Inst 2006;98:839–45). Shahinian observed that “financial incentives for the urologist … pressure from patients to prescribe something in the face of a cancer diagnosis, or influences from local opinion leaders” are all important factors guiding physicians’ decisions to use ADT.

“Pressure to use ADT is both pharmaceutical company driven and patient driven,” Studer said. “Drug companies sensitize patients with ads of happy older men on the golf course, which bypass doctors … without describing some of the side effects.”

Despite side effects, patients are often satisfied with ADT treatment. And despite more discomfort and reduced vitality experienced in ADT-treated patients, Potosky’s 2002 study confirmed that treated patients
were more satisfied with their treatment than those in the “watchful waiting” group. “It becomes a very hard sell to patients not to treat them,” Studer added. For some physicians, it may be faster and easier to give patients the hormones they believe will help them than to try to explain why they don’t need them, he said. “It takes 5 minutes to prescribe or give a drug, but it takes 45 minutes to explain why they don’t need it.”

In an editorial accompanying Potosky’s study, Talcott asked whether it is in fact justified to “just do something” in light of limited benefit and known risks of ADT (J Natl Cancer Inst 2002;94:407–9). Potosky and colleagues had reported that “[patients taking ADT drugs] reported a little more often being ‘pleased’ or ‘delighted’ with their treatment and to believe themselves free of cancer than the better-prognosis men who chose watchful waiting” despite serious toxic effects, Talcott wrote. He asked whether “doing something” that might not be beneficial to patients is justified in light of patient preferences.

Although nobody has a definitive answer to that question yet, the current evidence regarding survival rates suggests that in early, low-risk prostate cancer, doing nothing may trump doing something.

“I try to help patients move their thinking from the urgency of the moment to their future, looking back on their decision. I ask them to think about how they might feel with or without side effects of treatment and with and without cancer progression,” Talcott said. “Our job as doctors is to help patients understand the hand they’ve been dealt and give them options for how to play it. Not every hand merits betting the house.”