POINT/COUNTERPOINT

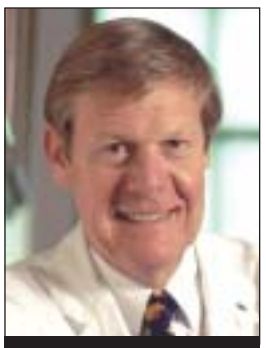
Should hormone treatment be started early in response to rising prostate-specific–antigen levels?

Why wait?

A raging controversy exists regarding the use of early vs. delayed hormone therapy and the use of chemotherapy for patients with rising prostate-specific–antigen levels after failed local therapy, or stage D1.5 disease.

Biochemical failure is common and can be lethal. In addition, there is a lot of PSA—patient-stimulated anxiety—that goes along with biochemical failure.

Of the 219,000 new cases of prostate cancer predicted to be diagnosed this year, many will be treated with local therapy, and about 50,000 will fail these local treatments and have biochemical failure. A subset of these 50,000 men will have rapid PSA doubling times, and will die as a result of biochemical failure.



E. DAVID CRAWFORD, M.D.

Biochemical failure studies from Johns Hopkins University in Baltimore showed that the median time to metastases is 8 years and the median time to death from metastatic disease is 5 years later (JAMA 1999;281:1591-7). How do we identify men who are at high risk of dying sooner? And can we intervene to make a difference?

PSA kinetics are important, for helping us identify patients at risk of early death, but there is no standard technique to determine PSA doubling time. Failure at less than 3 years, Gleason score of 8 or more, and a short doubling time (less than 3 months) are all important signs of heightened risk. However, there is no level 1 evidence available to tell us just what to do.

But I believe there is a role for early hormone therapy, because two-thirds of prostate cancer patients have disseminated disease. Hormone therapy often cures prostate cancer, but many men are undertreated. It is a fallacy to continue to believe that we can cure only local prostate cancers.

There are strong arguments favoring early therapy. Investigators have observed improved outcomes when early treatment is used for other cancer types, such as breast, lung, and colon. In our 1999 study, there was a huge difference in overall survival rate with immediate hormone treatment (N. Engl. J. Med. 1999;341:1781-8). Although it was a small study, the advantage is still there at 14 years.

Researchers opposed to early therapy highlight the side effect profile and often point to the lead-time bias that this represents. But basic biology supports the concept that radiation, chemotherapy, and surgery are most effective when the number of cancer cells is low. We have strong data telling us that people with rapid doubling times who fail early and have higher Gleason scores are likely to die from this disease.

So we can bury our heads in the sand and not do anything, or we can consider early hormone therapy for some patients. It may improve their outcomes, has psychological benefits, and without a doubt delays progression. ■

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What's the hurry?

It is important to look at the data and try to make the most rational decisions that we can make. Most of our current data on the use of hormones for rising PSA are derived from explanatory (phase I and phase II) trials. There have been some case reports of patients with rising PSA who were given some form of hormone therapy that lowered their PSA. In some cases, toxicity profiles associated with that approach also have been studied.

Pragmatic trials, on the other hand, seek to identify the best treatment available. Such trials require large numbers and long duration, and essentially reflect a comparison between new and established treatments. Based on published peer-reviewed data, we lack clear evidence that we need to give hormones early.

DEREK RAGHAVAN, M.D.

Some tumors may run indolent courses without any indication of metastasis for many years, whereas other, seemingly identical tumors may show evidence of occult progression, with slow PSA rise the only indicator of disease. Still other tumors diagnosed at a seemingly early stage may give rise to clinical metastases quickly, which may cause early death. It is important not to overtreat indolent disease with needless toxicity, but we must also avoid lethal undertreatment of aggressive prostate cancer.

Perhaps the key question is: "Is there evidence that early intervention alters overall survival?" No level 1 or randomized clinical trial evidence supports the use of early systemic therapy for rising PSA. The early studies of the Veterans Administration Cooperative Urological Research Group—notwithstanding important flaws of design and execution—failed to show any survival benefit from early use of estrogens or bilateral orchiectomy in addition to local therapy for early-stage disease (Cancer 1973;32:1126-30). Subsequent studies of early hormonal intervention for asymptomatic metastatic disease have shown no difference or only small differences in overall survival.

Systemic chemotherapy for metastatic disease, although promising, is also quite disappointing (N. Engl. J. Med. 2004;351:1513-20).The median and long-term survival figures are rather bleak, and hardly justify routine and unstructured application in early-stage disease.

In the past we've tended to look at hormones as being just an inconvenience, but we have underestimated the importance of the psychological and behavioral aspects of hormone therapy. We are now coming to understand more clearly the side effects, such as osteoporosis and metabolic syndrome, as well as other significant toxicities associated with hormone use in the context of rising PSA. Elegant conceptual and laboratory data suggest that it is reasonable to use hormones early. However, we have only a small amount of mature level 1 data, and no information that mandates early hormone therapy. ■

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Early Therapy Is Not Helpful for Recurrent Prostate Cancer

BY FRAN LOWRY
Orlando Bureau

Available evidence does not support the early use of androgen-deprivation therapy in men whose prostate cancer recurs after treatment, according to clinical practice guidelines issued by the American Society of Clinical Oncology.

In addressing the controversial issue, the ASCO guidelines recommend that hormone therapy be deferred in such patients until they experience symptoms of their disease.

The expert panel that drafted the document—an update of ASCO's 2004 guidelines for the initial management of androgen-sensitive prostate cancer that is metastatic, recurrent, or progressive—failed to find an overall survival advantage for early use of hormone therapy, compared with later use (J. Clin. Oncol. 2007 April 2 [Epub DOI:10.1200/JCO. 2006.10.1949]).

After performing a meta-analysis of seven studies that involved more than 5,000 patients, the panel concluded that early hormone therapy was associated with a 17% decrease in mortality from prostate cancer, but a 15% increase in mortality from other causes.

"Hormones are not benign. We have been thinking that they are bothersome because they cause hot flashes, fatigue, low sex drive, and thin bones. But the more we study this, the more aware we become that there are serious side effects associated with the hormones," lead author Dr. Andrew Loblaw said in an interview.

One of the most serious of these side effects is hip fracture due to osteoporosis. Many patients are unaware that a hip fracture increases mortality risk by 33% within the first month and 67% within the first year.

Doctors should discuss with their patients the risks and benefits of early hormone therapy, compared with deferred therapy.

'The more we study this, the more aware we become that there are serious side effects associated with the hormones.'

DR. LOBLAW

If a patient prefers to defer therapy, he should have regular visits with his physician every 3-6 months to monitor the disease, said Dr. Loblaw, of the Toronto-Sunnybrook Regional Cancer Centre, Toronto.

The panel suggested either bilateral orchiectomy or injections with luteinizing hormone-releasing hormone (LHRH) analogues as initial androgen-deprivation treatments. It also suggested that combined androgen blockade—nonsteroidal anti-androgen therapy with an orchiectomy or LHRH analogues—be considered for the treatment of locally advanced or metastatic prostate cancer.

It also stated that a newer nonsteroidal antiandrogen agent, bicalutamide, is preferable to older agents such as flutamide. "New data suggest bicalutamide combined with injection might improve survival by up to 20% and has fewer side effects, such as nausea and night blindness, than the older agents. Physicians should be aware of this," Dr. Loblaw said.

Still, he said, the struggle continues to distinguish the minority of men who will die from their prostate cancer from the majority of men who will die with it. "We know that prostate cancer kills 40,000 Americans and 4,000 Canadians every year, so we have to be able to separate out the bad actors." Dr. Loblaw and Canadian coinvestigators recently began accrual to the Early vs. Late Androgen Ablation Therapy (ELAAT) trial in the hope of doing just that.

ELAAT will enroll 11,000 patients who have recurrent prostate cancer after radiation therapy and will randomize them either to immediate hormone treatment or to hormone treatment once their prostate-specific–antigen level reaches 25 ng/mL.

"If men have symptoms after the cancer comes back, they should have hormone treatments. But the PSA when that occurs is around 100 [ng/mL]. So, we are only going to wait until the PSA rises to 25 [ng/mL]. It might be OK to wait, because hormone treatment has so many dangerous side effects," he said. ■