

Androgen Deprivation Therapy for Advanced Prostate Cancer: Can Evolution Be Accelerated?

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Physicians who treat cancer and the patients with cancer are often too busy or afraid, respectively, to stop and think about progress, or lack thereof, in the field. The request to write a thought piece on challenges experienced by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer (CaP) and the preparation of my talk for the NCCN 21st Annual Conference caused me to stop and think about androgen deprivation therapy (ADT). ADT is something that I have spent my research career attempting to understand from the perspective of the CaP cell.

An optimist would say that we have many new agents to offer men with castration-recurrent/castration-resistant CaP (CRPC), including docetaxel (FDA-approved May 19, 2004), sipuleucel-T (FDA-approved April 26, 2010), cabazitaxel (FDA-approved June 17, 2012), enzalutamide (FDA-approved August 31, 2012), abiraterone acetate (FDA-approved December 10, 2012), and Rad-223 (FDA-approved May 15, 2013). These were approved based on extensions of survival of 2.4, 4.1, 2.4, 4.8, 4.0, and 3.6 months, respectively. A pessimist would hold that almost all men die of CaP once it becomes castration-recurrent, and survival is extended by only approximately 2 years at a cost of approximately \$500,000, if each agent was used sequentially for the mean duration that the agent was used in its registration trial.

FDA approval for these agents was facilitated because clinical trials were conducted in a cost- and time-efficient manner—because patient survival is limited—and because the FDA accepts the oncologic end point of overall survival. Medical oncologists are grateful for new targets for intervention, provided through translational research. Possible interventions include chemotherapy to address rapidly proliferating cells, CYP17A1 inhibitors to address intracrine androgen metabolism, and small molecule androgen receptor inhibitors, which more effectively compete with dihydrotestosterone for the androgen receptor ligand-binding domain. The NCCN Prostate Cancer Panel has responded by releasing as many as 3 updates each year to coincide with FDA approvals or publication of results of successful phase III clinical trials. American men seem grateful for these new agents that prolong survival, although these agents are costly to our health care system (and increasingly to patients themselves through larger copays).

Compared with CRPC, far greater number of men undergo potentially curative CaP treatment and experience biochemical recurrence. These men are faced with uncertainty about the relative costs, risks, and benefits of salvage local therapies or early application of ADT. ADT has been used in a neoadjuvant/concurrent/adjuvant fashion to improve the results of radiation for high-risk CaP, and survival benefit has been shown when ADT is used for 2 or 3 years. However, the improvement in survival is relatively modest, and the side effects of ADT for 2 or 3 years are considerable.

A biomarker of response to ADT when used in conjunction with radiation therapy would enable a more personalized approach to ADT and determining its optimal duration. In similar fashion, controversy remains about the timing and duration of ADT when local therapy has failed. Most believe that early ADT is best, but early ADT is associated with increased side effects and the development of metabolic syndrome. Most medical oncologists favor early ADT and most urologists favor later ADT.



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A review of the older literature from both clinical practice and preclinical models provides little evidence that the timing of ADT matters. The most elegant research on this subject comes from Messing et al's¹ SWOG trial of men found to have lymph node metastases at radical prostatectomy. A total of 98 patients were randomized to immediate continuous ADT or observation. In the immediate ADT arm of 47 patients, 30 remained alive, 29 of whom were recurrence-free and 26 of whom were prostate-specific antigen failure-free after a median follow-up of 11.9 years (range, 9.7–14.5 years for survivors).^{1,2} However, the authors cannot explain why the results were so good. In fact, these results fly in the face of a population-based test of ADT published subsequently.³

Wong et al³ reported on a SEER-Medicare–based study of men who underwent radical prostatectomy and had positive lymph nodes. The study used propensity matching to compare men who received ADT within 120 days versus those who underwent observation. The 2 groups had similar median and range of follow-up for survivors, but overall survival and CaP-specific survival were similar. However, continuous ADT remains the standard of care for men found to have lymph node metastases at the time of radical prostatectomy. The Messing trial has been cited repeatedly to justify early ADT. The Messing study occurred before the PSA era, but it is similar to the Wong study in almost all other respects. Among these studies, one involving 98 men showed almost unbelievable benefit^{1,2} and a population-based study involving 731 men showed no benefit.³

So how does the field resolve a contradiction as simple as this? Some in the field have called for a phase III clinical trial of ADT in men found to have lymph node metastases at radical prostatectomy. However, such a trial would be prohibitively expensive because it would require hundreds of men to be accrued after thousands of radical prostatectomies. In addition, the average time from lymph node metastasis to bone metastasis is 3 years, and survival is approximately 3 more years with ADT and perhaps 5 more years with ADT and new agents.

A similar argument can be made about studying differences between continuous and intermittent ADT. Again, medical oncologists usually prefer continuous ADT, but many urologists use intermittent ADT preferentially, especially in more favorable disease. A meta-analysis of 6 randomized clinical trials selected from a total of 26 published trials concluded that mortality was similar for intermittent and continuous ADT and that quality of life was better for intermittent ADT.⁴ The difficulty of assessing quality of life is demonstrated by SWOG 9346.^{5,6} Erectile function and mental health results were better at 3 months off ADT in cycle 1. However, the cumulative incidence 10 years later among 636 Medicare beneficiaries was similar for elevated cholesterol levels, osteoporosis, dementia, depression, and erectile function but ischemic and thrombotic events occurred in 24% of patients in the continuous ADT arm and 33% in the intermittent ADT arm. Quality of life studies are difficult to conduct and interpret. For example, it is surprising that only 6% of Medicare beneficiaries on intermittent or continuous ADT experienced erectile dysfunction 10 years after study enrollment. A more careful quality of life study of continuous versus intermittent ADT would require randomization of at least 1,000 patients. However, we cannot reliably determine the proper duration of induction ADT, the PSA level that warrants reinitiation of ADT, and the PSA level that warrants stopping ADT because the clinical trials differ and no clinical consensus exists. Thus, design of such a trial would be so problematic and its conduct so expensive that the timing and duration of induction and intermittent ADT probably would remain contentious.

Is there a better way to inform our guidelines when we require high-level evidence? I propose that continuing to conduct series of large, expensive—and by the time they are completed, perhaps irrelevant—phase III clinical trials is not the best way

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forward. Phase III clinical trials also increase the expense of bringing a drug to market, which is one of the factors leading to the explosion in costs of new cancer drugs. Drug development, medical oncology, the American health care system, the FDA, and patients with cancer may wish to consider that manufacturers of automobiles, electronics, airplanes, and, in an extreme example, parachutes do not conduct large, randomized trials to determine whether a new product is better than a current product. These industries use statistical process control, a methodology that assumes that the variation in a system lies within certain limits or tolerance intervals.⁷ A change in a product (ie, drug) that either worsens or improves the project will produce a special cause variation that lies outside the previously established limits. Nelson's rules for interpreting statistical process control data allow recognition of an improvement or a decrement with limited numbers of observations (typically about 25).

Statistical process control would be more economical than the adaptive multiarm, multistage, platform-randomized, controlled phase II/III STAMPEDE trial that helped define the role of docetaxel in addition to ADT for advanced CaP.⁸ For example, evidence in low-volume disease differs among studies such as GETUG-AFU,⁹ CHAARTED,¹⁰ and the various arms of STAMPEDE, and may not be resolved because of differences in eligibility, type, and duration of ADT, and differences in and tolerances of docetaxel regimens. Statistical process control could better define which patients would benefit from docetaxel combined with ADT for advanced CaP better than is happening currently.

In summary, treating advanced CaP has come a long way since Dr. Huggins demonstrated in 1941 that CaP regressed after surgical castration. However, too many men still die of CaP. We still see many knowledge deficits when critically examining a given recommendation or the evidence on which it is based. More rapid improvement may be possible if we learn from the manufacturing industry how to more efficiently evaluate new interventions.

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