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Hitting old targets better and identifying new targets

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Abstract

Options to treat late-stage castration-resistant prostate cancer continued to increase in 2011, as three agents with different mechanisms of action prolonged life and a fourth reduced the morbidity of skeletal metastases. These outcomes contrasted with the heightened controversy generated by the recommendation against PSA screening and other early detection strategies.

In the Western world, one in six men will be diagnosed with prostate cancer and, of these, one in six will die of metastatic disease. Improving outcomes for men with prostate cancer depends on the one hand on developing more-effective systemic therapies and, on the other hand, on early diagnosis and treatment, before the disease has metastasized.

2011 is the 70th anniversary of when Charles Huggins established that prostate cancer is an androgen-dependent malignancy and, until recently, docetaxel was the only non-hormonal therapy to prolong life. In 2010, sipuleucel-T and cabazitaxel were shown to confer a survival benefit and were subsequently approved by the FDA. This trend continued in 2011, as three therapies, CYP17 inhibitor abiraterone acetate,¹ bone-targeting agent radium-223,² and androgen-signaling inhibitor MDV3100,³ were shown to prolong life in definitive phase III clinical trials (Figure 1), and the RANKL inhibitor, denosumab, was shown to be superior to zoledronic acid in reducing the morbidity associated with bone metastases.⁴ The demonstration that agents targeting unique aspects of the malignant process associated with tumor cell growth and survival could provide meaningful clinical benefits has highlighted the importance of understanding the biology of castration-resistant prostate cancer (CRPC). The trials established important principles, which will be discussed.

The first principle is that CRPCs are not hormone refractory. CRPCs acquire diverse mechanisms to reactivate the androgen receptor signaling pathway in the environment of castrate levels of androgens, including an increase in the androgen biosynthetic machinery and overexpression of androgen receptor. Thus, further decreasing androgen levels by inhibiting steroid synthesis enzymes in the adrenal glands and tumor may be of benefit. CYP17 is a cytochrome P450 enzyme that catalyzes the rate-limiting step of androgen synthesis; abiraterone acetate is a structural analog of the CYP17 substrate pregnenolone

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Competing interests

H. I. Scher declares associations with the following companies: Amgen, Dendreon, Exelixis, Medivation, Ortho Biotech Oncology Research & Development, Sanofi-Aventis. See the article online for full details of the relationships. Y. Chen declares no competing interests.

that is rationally designed to be a specific and irreversible inhibitor of CYP17. A large international phase III trial (Cougar AA-301) that compared abiraterone acetate plus prednisone (to prevent mineralocorticoid excess) and placebo plus prednisone in patients with CRPC who had received docetaxel showed an increase in median overall survival from 10.9 to 14.8 months (hazard ratio = 0.65; $P < 0.001$).¹ All major subgroups of patients benefitted and treatment was well tolerated. A separate trial assessing abiraterone acetate in chemotherapy-naïve patients has completed accrual and the results are awaited (NCT00887198).

Another drug supporting the principle that CRPCs are not hormone refractory is MDV3100, a next-generation anti-androgen that was rationally designed to overcome several deficiencies of available agents including modest receptor binding and agonist properties that can promote tumor growth. The drug displays no androgen receptor activation, blocks nuclear translocation of the receptor and completely inhibits the ability of androgen receptor to bind to DNA.³ Promising activity of MDV3100 was demonstrated in a phase I–II trial in 140 patients, which led to the phase III AFFIRM trial in patients with chemotherapy-treated CRPC that compared MDV3100 with placebo.³ This trial was stopped by the Data Safety and Monitoring Board in November 2011 when the first planned interim analysis showed a 37% reduction in mortality, and superior overall survival (median 18.4 versus 13.6 months) in favor of MDV3100.³

The second principle was that targeting the bone environment can confer benefits, independent of an effect on prostate-specific antigen (PSA). Bone is the most common site of prostate cancer spread and is responsible for the highest morbidity burden from the disease. Therapies directed at the bone microenvironment can be divided into three classes: osteoclast inhibitors of bone resorption, radiopharmaceuticals that target bone, and kinase inhibitors. Despite the radiographic appearance of osteoblastic lesions, there is heightened osteoclastic activity and bone turnover in metastatic prostate cancer lesions. Osteoclast inhibitors, including zoledronic acid, are used as an adjuvant therapy to maintain bone density and to decrease skeletal-related events (SRE) in patients with CRPC. Denosumab is a humanized monoclonal antibody that blocks RANKL, which is required for osteoclast activation and survival. In 1,904 patients with CRPC that had metastasized to the bone, denosumab delayed the median time to first SRE from 17.1 to 20.7 months ($P = 0.008$) compared to zoledronic acid, leading to FDA approval.⁴

The beta-emitting bone-seeking radioisotopes strontium-89 and samarium-153 lexidronam are approved for the palliation of pain, but neither has been shown to prolong life. Radium-223 is a unique bone-directed radioisotope that emits high-energy alpha particles that penetrate only several cell layers in tissue, significantly improving the radiation delivery to areas of sclerotic bone where the tumor resides while minimizing radiation to hematopoietic tissue. In a phase III trial in 922 patients with CRPC and bone pain, 6-monthly doses of radium-223 conferred a significant overall survival benefit over placebo (14.0 versus 11.2 months; $P = 0.00185$);² it is the first bone-directed agent to prolong overall survival.

Multiple signaling cascades are critical for bone homeostasis and turnover. Two promising investigational agents targeting this axis deserve mention. Dasatinib inhibits kinases including Src family tyrosine kinases that are important for bone turnover; a single-agent phase II trial in patients with CRPC showed a marked decrease in bone turnover, disease stabilization⁵ and additive effects with docetaxel. A phase III trial comparing dasatinib with placebo in combination with docetaxel has completed accrual. Cabozantinib inhibits kinases including Ret, Met, and VEGFR2; in a randomized phase III discontinuation trial in patients with CRPC, treatment with cabozantinib was associated with normalization of radionuclide bone scans in 86% of patients, improvement of bone pain in 64% of patients, decline in bone marker levels, improvement of anemia, and a marked reduction in bone pain independent of an effect on PSA.⁶ Two phase III trials will be opened for recruitment soon: the first for an indication for the palliation of pain and a second for an improvement in overall survival in patients with CRPC.

Limiting the use of agents shown to prolong life to men with advanced metastatic CRPC will not considerably decrease the number of men who die from prostate cancer. To do so requires the identification and treatment of those cancers that are destined to metastasize, produce symptoms and ultimately shorten a patient's anticipated life expectancy when tumor burdens are minimal. With this goal but without firm evidence, the advent of the PSA test led to widespread screening that has been accompanied by a marked increase in men diagnosed with localized disease who undergo radical prostatectomy and definitive radiotherapy with the associated morbidities. Over the past 2 years, the US PLCO trial showed no reduction in prostate cancer-specific mortality (PCSM) at 7-years after the initiation of PSA screening; the European Randomized Study of Screening for Prostate Cancer showed a 20% decrease in PCSM at 9 years after the initiation of PSA screening; and the Göteborg randomized screening trial showed a 44% decrease in PCSM at 14 years after the initiation of screening.⁷⁻⁹ These results, along with an analysis of other early detection studies led the USPSTF to recommend against PSA screening because of "moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits."¹⁰ The recommendation triggered a firestorm of debate, proponents of screening highlighting flaws in methodology and interpretation and opponents the limited benefits, anxiety and morbidity a diagnosis produces, and the high societal costs.

There is strong evidence prostatectomy and radiotherapy can decrease PCSM by approximately 50% in clinically localized disease. However, in low-risk disease where the 15-year PCSM is <2%, these benefits become tiny, especially in those with limited longevity. Despite this, more than half of the men treated with prostatectomy and radiotherapy in the USA have low-risk disease. It is important to note that the harms of screening come not from the PSA test, but from the chain of actions following PSA measurement. It has been ingrained into the psyche of physicians and patients that all cancers are rapidly lethal unless treated aggressively. The USPSTF recommendation is an appropriate pushback against non-discriminate screening and subsequent treatment and argues that early detection strategies focus on diagnosing cancers that need treatment to reduce morbidity and mortality, and avoid finding highly prevalent indolent cancers for which any treatment is overtreatment. The two overarching objectives in the field are to decrease death and suffering but, at the same time, decrease those who are subjected to

unnecessary treatment that can produce significant morbidity. It is clear that neither our current practice pattern nor the blanket discontinuation of PSA screening can adequately address these goals. The benefit-to-harm ratio can be shifted if both screening and treatment are targeted to high-risk populations and surveillance becomes more widely adopted for non-aggressive localized tumors.

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Key advances

- Abiraterone acetate and MDV3100 prolong overall survival in patients with docetaxel-treated castration-resistant prostate cancer (CRPC)^{1,3}
- Radium-223 prolongs overall survival in patients with CRPC, bone pain from disease, and who are docetaxel-treated or ineligible for docetaxel treatment²
- Denosumab delays skeletal-related events compared with zoledronic acid in patients with CRPC and bone disease⁴