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PCa Commentary

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AN ALTERNATIVE TO LUPRON - "The Road Not Taken"

"... and I took the one less traveled by, and that has made all the difference."
(Apologies to Robert Frost)

The quest for effective alternative therapies that avoid the toxicity of long-term Lupron exposure in the treatment of high-risk or relapsing prostate cancer has spawned several well recognized options. Among them are: 6 months of Lupron therapy (as opposed to longer-term usage) for selected patients predicted to be less likely to fail; intermittent androgen deprivation (ADT) with interval "free periods" using a PSA threshold as a trigger for restarting treatment; and intermittent ADT, restarting suppression after "free periods" at a chosen testosterone level.

A report by Small, Vogelzang, et al. highlights a less acknowledged option: "Efficacy of peripheral androgen blockage in prostate cancer patients with biochemical failure after definitive local therapy: Results of Cancer and Leukemia Group B (CALGB) 9782," *CANCER,* Dec 2011. The CALGB regimen consisted of finasteride (Proscar) 5 mg/day combined with flutamide (Eulexin) 250 mg 3X/day. Today the combination would likely be dutasteride (Avodart), 0.5 mg (or 3.5 mg) daily, with bicalutamide (Casodex) 50 mg/day.

"All patients had undergone previous definitive therapy and had evidence of a rising PSA >1ng/mL, with no evidence of recurrent disease." Ninety-nine men were followed for a median of 10 years and the median survival time has not been reached. A PSA decline of >80% was seen in 96% of the men. The 5-year overall survival was 87% and the toxicity was mild. Earlier trials showed that in most men after PSA failure on this regimen control could be regained by Lupron administration.

Because of using non-current medications, the CALGB study should be considered only as a "proof of principle." Studies are now testing the combination of dutasteride/bicalutamide, and in time may possibly employ the super-antiandrogen, MDV3100, to replace Casodex. Interest in the 5α-reductase/antiandrogen regimen is driven by concern for quality of life issues. *This combination does not lower serum testosterone.* Simultaneously, it *does* lower intraprostatic dihydrotestosterone (DHT), the androgen 10-20 times more potent than testosterone in activating the androgen receptor. The combination also results in a >70% decline in serum DHT levels.

Dutasteride at 0.5 mg (based on work by Martin Gleeve and others) lowers intraprostatic DHT by 94%, and 3.5 mg drops it by 99%. Despite a moderate compensatory rise of testosterone in prostate cells, the total androgen drive in the prostate is lessened. Because of differing bodily tissue specificities (e.g. in muscle, bone, and brain) for testosterone as compared to DHT, important biologic systems remain functional in the presence of maintained serum T levels, and are not impaired by depleted serum DHT. Those systems are crucial for the quality of life issues, i.e. muscle vitality, bone mineral preservation, erectile function and libido, and maintenance of mood and cognition.

There are two conventionally recognized 5α-reductase enzymes (now three), 5α-R1 and 5α-R2. Dutasteride inhibits both while finasteride works only against enzyme 2. In benign prostate tissue, enzyme 2 is predominant, but in prostate cancer cells enzyme 1 is ascendant and *increases* as cells become more aggressive, supporting the expectation that dutasteride will function more effectively against prostate cancer.

What lies ahead in this field? Important clinical guidance is expected from NIH trial NCT00470834 which is ongoing but not recruiting: "Prostate Cancer Study in Men Who Have Failed First-Line Androgen Deprivation Therapy." The study compares Casodex 50mg daily plus placebo to Casodex 50 mg plus dutasteride 3.5 mg and addresses the question as to whether dutasteride will augment and prolong bicalutamide's efficacy.

BOTTOM LINE: Stay tuned. The results of the NIH trial will likely alter clinical management. The preservation of "quality of life" has become an important component in decisions regarding the best therapy and a 5α-reductase/anti-androgen combination is emerging as an option to be considered.

MDV3100 - Phase III "AFFIRM" Trial Demonstrates Survival Benefit.

At the February 2012 Genitourinary Cancer Symposium Howard Scher reported the ultimate "proof of principle" trial data: An estimated 18.4 month overall survival for men treated with MDV3100 compared to 13.6 months for men treated by a placebo — a reduction in risk of death of 37%.

The study was composed of 1,199 men with castrate resistant prostate cancer (CRPC) who were progressing after 2 or more regimens of Taxotere chemotherapy. These encouraging results are likely to secure MDV3100, when FDA approved, a pivotal role in the therapy of relapsed prostate cancer.

Think of MDV3100 as a "supercharged" Casodex. Bicalutamide (Casodex) has proven to be an effective drug, but its function in inhibiting activation of the androgen receptor (AR) is limited by being 30 times weaker than dihydrotestosterone, the natural ligand, in the competition for AR binding. MDV3100 is a significantly more effective inhibitor of AR function than bicalutamide.

In the journal *SCIENCE*, May 8, 2009, Sawyers, Higano, Beer, et al. describe their elegant basic science studies setting forth the rational development of MDV3100, its mechanism of action and the basis for its superiority over bicalutamide.

Important points established in their research include:

- It is well recognized that in castrate-resistant prostate cancer expression of the androgen receptor is *increased*. This overexpression of receptors constitutes an increased challenge to the receptor-blocking action of antiandrogens, particularly for bicalutamide, due to its substantially weaker affinity for the receptor compared to DHT. Sawyers' research demonstrated that the greater receptor affinity of MDV3100 partially overcomes the consequences of this overexpression.

- To effect gene expression the activated AR must bind to DNA and also recruit assistance from "co-activators." Research showed that MDV3100 inhibits both processes.

- Over time the AR adjusts to partial bicalutamide antagonism and, paradoxically, bicalutamide becomes an AR activator itself, i.e. an agonist. This reversal is the basis of the phenomenon of the "androgen withdrawal" response wherein ~30% of men show a PSA decline after bicalutamide treatment is stopped. The research by Sawyers established that during continued usage MDV3100 "does not display agonism in AR-overexpressing cells."

- In order for an activated AR to promote gene expression the receptor must move from the cytoplasm into the cell nucleus to encounter DNA. Again, the research indicated that MDV3100 prevents this nuclear transition five-fold more effectively than bicalutamide.

BOTTOM LINE: Current evidence strongly supports that MDV3100 will become an important therapeutic option for the treatment of men with relapsed prostate cancer. In the future this drug will possibly find a role in earlier stages of the disease, either alone or in combination with other agents. The primary question now is how to combine or sequence abiraterone, MDV3100 and taxanes to exploit mechanisms of resistance to these agents.

ABIRATERONE: A Brief Update

It is generally anticipated that the recently FDA approved drug, abiraterone ("*Zytiga"),* will find its principle therapeutic indication "moved up front" for usage in men who display castrate-resistant prostate cancer (CRPC). Currently the drug is only FDA approved for treatment in men with CRPC progressing *after* chemotherapy with docetaxel ("Taxotere"). Approval was based on the trial demonstrating a survival extension in men with metastatic CRPC to 14.8 months for abiraterone therapy compared to 10.9 months for placebo treatment.

Encouragement for the anticipated earlier use of abiraterone is presented by Small, Ryan, et al, (*Clinical Cancer Research, 2011 Jul): "*Phase II study of abiraterone in chemotherapy-naive metastatic castrate-resistant prostate cancer displaying bone flare discordant with serologic response."

This study was important for two reasons:

(1) it demonstrated effectiveness for the drug in this earlier setting (i.e. before chemotherapy), and
(2) again demonstrated that increased activity in early follow-up bone scans most likely is a sign of bone healing as opposed to disease progression.

RESULTS: A PSA decline of 50% or more was seen in 79% of the 33 men on study. The median time to PSA progression was 16.3 months.

Bone scans performed 3 months after therapy initiation in 50% of men (12/23) were initially read as showing "disease progression" *despite a PSA decline of more than 50%*. Subsequently the bone scans in 11 of these 12 men showed improvement or stability.

Basic science studies have confirmed that prostate cancer cells carry all the essential enzymes - notably CYP17A1 - to generate androgens from basic building blocks. The newest work now confirms the activity of this system in metastatic prostate cancer cells retrieved from bone metastases.

Research is already progressing toward understanding the mechanism of resistance to abiraterone. Mostaghel, Nelson, Montgomery et al., working at the Fred Hutchinson Cancer Research Center and the University of Washington (*Clinical Cancer Research,* Aug 2011), established that some cancer cells overexpress the CYP enzyme and present a greater obstacle for abiraterone inhibition. Other cells develop mutations that bypass the system entirely. They speculate that a higher dose of abiraterone may be necessary to overcome resistance in the presence of CYP-rich environment.

In Case You Are Wondering:

"Why is it necessary to continue an LHRH agonist (i.e. Lupron) in CRPC patients when prescribing abiraterone?" ⇨ *Explanation:* When used as a single agent, abiraterone significantly lowers the levels of serum testosterone and intraprostatic androgens. However, a compensatory increase in pituitary luteinizing hormone shortly follows, raising the serum testosterone and mitigating the benefit of its decline. This effect is prevented by an LHRH agonist or antagonist. To date there have been no studies of abiraterone unaccompanied by a LHRH agonist in patients with CRPC.

"Why is it advisable to co-administer a corticosteroid (i.e. 0.5 mg dexamethasone or prednisone 5 mg once or twice daily)?" ⇨ *Explanation:* While abiraterone inhibits the function of CYP17A1, a pivotal enzyme in enabling the cellular production of testosterone and dihydrotestosterone, the blockage of this enzyme results in a compensatory rise of pituitary adrenocorticotropic hormone (ACTH). The consequence of ACTH increase is the production of steroids that cause hypertension, potassium depletion, and fluid retention. Dexamethasone or prednisone suppress the rise in ACTH, blunting, but not completely blocking the developments of these complications.

BOTTOM LINE: Abiraterone will most certainly assume an important role in the treatment of prostate cancer. Its optimal position in therapy sequencing is under intense investigation.

"ALPHARADIN" (RADIUM-223 CHLORIDE):
A NEW TREATMENT FOR BONE METASTASES - Fast Tracked for FDA Approval.

At the February 2012 Genitourinary Symposium Oliver Sartor reported the very promising results of a Phase III trial of this new radiopharmaceutical, an alpha emitting agent that *nearly selectively* targets metastatic prostate cells in bone and the surrounding stroma. Currently available bone targeting agents, i.e. Samarium, lack tumor/stroma specificity and their effectiveness is compromised due to marrow damage resulting in impaired cellular production, limiting the use of chemotherapy.

"Alpharadin" is administered intravenously. It achieves specificity by homing to bone marrow calcium, which is enriched in the developing osteoblastic lesions of early cancer spread. The alpha particle (two neutrons and two protons) emits short-range radiation spanning two to ten cell diameters causing double-strand breaks in DNA and cell death.

Trial Results: "Alpharadin," when compared to its use in patients receiving a placebo, reduced pathologic fractures and spinal cord compressions by one half and reduced the need for radiation therapy by one third. The trial involved 922 men with castrate-resistant prostate cancer with two or more symptomatic bone metastases.

The interval to the first skeletal event occurring *after* the initiation of therapy with Radium-223 was extended to 13.6 compared to 8.4 months (placebo), a 39% improvement. To date leukopenia has not been seen with the agent.

BOTTOM LINE: The forthcoming availability of both "Alpharadin," and carbozantinib, another promising drug that has shown remarkable effectiveness against bone metastases in early trials (see PCa Commentary, Sept/Oct 2011 for discussion), is very good news for the many men who have prostate cancer spread to their bones.

DENOSUMAB:
An effective agent to prevent progression of bone metastases.

For treatment of prostate cancer spread to bone, denosumab (trade names: Xgeva, Prolia) is the new boy on the block - compared to the long-time resident, zoledronic acid (Zometa). In recent months there has been an "abundance of riches" with reports of encouraging trials of denosumab. The quest now is finding the optimal position of this drug in the sequence of treatment.

As background, it's useful to review the mechanisms by which these two drugs interrupt cancerous bone destruction. Prostate cancer preferentially homes to bone. The vast majority of men who have *not been cured* by primary therapy will likely experience metastatic spread to bone at some time in the course of their disease. When spread occurs, metastatic cells settle into a prepared niche in the bone marrow, begin a two-way communication with the surrounding microenvironment, activate osteoblasts, which in turn initiate bone destruction by osteoclasts. The stimulated osteoblast secretes a messenger, RANK ligand (RANKL) which promotes osteoclastic bone lysis.

Both drugs interrupt this process of bone destruction, each doing so in its own way. **Zoledronic acid** inhibits tumor cell adhesion to bone, inhibits osteoclastic activity, and induces death of osteoclasts. **Denosumab**, a monoclonal antibody, binds to RANKL en route to osteoclasts, neutralizes RANKL's activity, and prevents the osteoclastic bone resorption.

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DENOSUMAB continued:

Xgeva is administered subcutaneously 120 mg. every 4 weeks; Zometa, intravenously 4 mg every 4 weeks. Zometa can impair kidney function and monitoring is required. Both can lead to hypocalcemia. Both are associated with low incidence of osteonecrosis of the jaw (ONJ): Zometa about 1-2%; Xgeva, ~ 2-5%.

Now the line-up of indications:

- Xgeva can be used to treat osteoporosis independent of cancer. For this indication the dose is 60 mg once or twice yearly.

- Xgeva is FDA approved for use to prevent bone loss in men receiving androgen-deprivation therapy (ADT) for non-metastatic prostate cancer (Smith, *NEJM*, August 20, 2009). This study evaluated Xgeva's effect on bone mineral density (BMD) and in prevention of fractures. The dose is 60 mg every 6 months.

  Results: At 24 months the BMD in the lumber spine in the Xgeva group increased 5.6% versus a loss of 1.0% for placebo therapy. New vertebral fractures developed in 1.5% of men compared to 3.9% for placebo.

- Xgeva was compared to Zometa in a trial of treatment for men with bone metastases from castrate-resistant prostate cancer (Fizazi, *Lancet,* Mar 2011). In this study a skeletal related event (SRE), i.e. a pathologic fracture, spinal cord compression, or surgery or radiation to bone, had already occurred in each man.

  - The primary study endpoint was time to first subsequent on-study SRE.
  - Xgeva was dosed at 120 mg and Zometa at 4 mg both every 4 weeks.
  - Median time to first SRE for Xgeva was 20.7 months; for Zometa, 17.1 months.
  - Hypocalcemia developed in 13% of men on Xgeva v. 6%, Zometa; ONJ 2% for Xgeva v. 1% for Zometa. Xgeva is FDA approved for this indication.

  A Phase II study (Fiazi, *JCO,* Apr 2009) showed that denosumab could regain control of bone destruction in men whose bone turnover markers indicated increasing osteolysis despite Zometa treatment.

- The most recent study findings were reported at the February 2012 Genitourinary Cancer Symposium: *"Effect of denosumab on prolonging bone-metastases free survival (BMFS) in men with non-metastatic castrate-resistant prostate cancer presenting with aggressive PSA kinetics."* Denosumab dose: 120 mg every 4 weeks.

  The findings: A previous study (Smith, *Lancet, Jan 2012)* had already established that denosumab prolonged bone metastases-free survival (BMFS) by 4.2 months (29.5 v. 25.2 months) in a group of men with non-metastatic CRPC versus placebo *in men at high risk* for bone metastases (PSA ≥8 ng/ml and/or PSA doubling time [PSADT] ≤10.0 months).

  The new study reported at the 2012 symposium further narrowed the definition of high-risk to focus only on those men at even *higher risk*: PSADT <6 months.

  - The study endpoint was time to first evidence of bone metastases or death.
  - In the denosumab group the median BMFS was prolonged by 7.2 months (25.2 months, compared to placebo, 18.7 months) - a 23% reduction compared to the 4.2 months delay reported earlier in the *Lancet* report that studied men at slightly less risk for progression of bone-metastases.

continued

DENOSUMAB continued:

The FDA's Oncologic Drugs Advisory Committee recently voted 12-1 *against* expanding the approved indication for denosumab for use in men with no metastases basing their opinion on the Lancet study's reported 4.2 months benefit. Also of FDA concern was the 5% incidence ONJ for denosumab compared to none in the placebo group. It will be interesting to see if the most recent data based on limiting treatment to men with PSADT of <6 months will alter that opinion.

Xgeva and Zometa are pricey drugs. "Using published wholesale cost, denosumab costs $16,830 and zoledronic acid, $8,321, for 12 months at full adherence" (M*edpage Today,* Sept 11, 2011). However, an uninsured person receiving the drugs in a hospital setting might well see a charge of *three or even four times* those figures. For Zometa there are additional costs for intravenous administration and monitoring renal function.

Perhaps the advisory committee's negative vote might be partially explained by the relative cost of Xgeva and the speculation that the benefit accrued by "preventive" use *before a SRE* might not improve upon the ultimate gain compared to its use *after* the first SRE.

BOTTOM LINE: Denosumab and zoledronic acid have both shown effectiveness in delaying further progression of bone destruction from metastatic prostate cancer. The optimal timing and dosing of their administration are under continuing study.

Your comments and requests for information on a specific topic are welcome at **ecweber@nwlink.com**

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