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SPECIAL ISSUE

TWO PROMISING NEW AGENTS IN LATE CLINICAL TRIALS: ABIRATERONE AND DENOSOMAB

HORMONE INTERVENTION: ABIRATERONE: A Hormone Therapy for "Hormone Refractory" Prostate Cancer - An Introduction

A rock solid research finding in recent years is that androgen signaling via the androgen receptor (AR) continues and gradually *increases* during androgen deprivation therapy (ADT) creating the therapeutic dilemma of an "androgen refractory" state. In fact, the lead article in the first issue of the PCa Commentary, October 2002, highlighted this fact, pointing out that in the latter phases of ADT many of the androgen responsive genes that had been *initially suppressed* by ADT become reactivated as "hormone resistance" develops. The best recognized gene being the marker, PSA. Multiple studies have demonstrated that in response to the castrate levels of testosterone the AR gene is *amplified* in 25-30% of men with CRPC compared with 1-2% in men with localized disease. This increase in gene copies is associated with an overall greater sensitivity to androgens despite low levels of serum testosterone resulting from androgen deprivation therapy (ADT). Additionally, mutations in the AR gene produce changes in the structure of the receptor's ligand pocket broadening its acceptance of other steroids, i.e. progesterone, estradiol, and adrenal androgenic steroids.

Castrate-resistant prostate cancer (CRPC) tumor cells contain all the enzymes necessary for androgen synthesis *de novo* from the earliest steroid building blocks, such as cholesterol, to the final androgen product, dihydrotestosterone (DHT). Utilizing these enzymes tumor cells can complete the construction

of DHT by converting androgenic steroids synthesized by the adrenal gland. Continued effective androgen receptor signaling unrestrained by castrate levels of testosterone and other hormonal manipulations has, in frustration (and now misleadingly), been termed the "androgen refractory" state, usually defined as a rising PSA despite several regimens of attempted hormonal control. Abiraterone is about to change that paradigm.

Abiraterone, a forthcoming drug well along in the clinical trials pipeline, has the potential of providing clinicians with the means of significantly *extending* hormonal control of prostate cancer beyond "hormone refractoriness." Abiraterone is an irreversible steroidal inhibitor targeting the enzyme CYP17 thereby blocking two vital reactions in the chain of sequential conversions that progress through intermediate steroids and finally to androgens and estrogens. This metabolic pathway to testosterone can take place not only in the adrenal glands and the Leydig cells, but also *endogenously* in prostate cells, benign and malignant. By inhibiting CYP17, abiraterone renders serum testosterone "undetectable."

Unfortunately, the abiraterone induced enzymatic block causes unwanted side effects. The "pre-block" CYP17 steroids build up like a reservoir filling behind a dam; whereas cortisol, a "post-block" steroid, is diminished, and its paucity interrupts negative feedback control of pituitary generated adrenocorticotropic hormone, ACTH. ACTH secretion increases, resulting in the excessive build up of the pre-block steroids - notably the adrenal mineralocorticoid, aldosterone. The consequent side effects: hypokalemia, hypertension, and fluid retention.

The overproduced "up-stream" steroids deoxycorticosterone and corticosterone themselves have the unwelcome capacity to activate the AR. Fortunately, small doses of decadron or prednisone can re-establish feedback control of ACTH, represses its generation, and diminishes the side effects. In Phase II studies Decadron was added and in the ongoing Phase III trial prednisone is employed.

When disease progression occurred despite continued abiraterone therapy the marked repression of androgens and estrogens was maintained, suggesting that other mechanisms of AR activation now explain the PSA rise.

"Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms that Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven (Attard et al., JCO Oct 1, 2008 - pre-released online). The study subjects were resistant to *multiple prior hormonal therapies* including antiandrogens. LHRH agonists were continued. In 21 patients "PSA declines of $\geq$50% lasting for longer than three months from the start of treatment were observed in 57% of CRPC patients, while 66, 42, and 29% of patients had $\geq$30, $\geq$75, and $\geq$90% PSA declines, respectively, which lasted between 69 and 578+ days.

A Phase II trial in chemotherapy-naive patients was conducted jointly at the Royal Marsden Hospital (UK) and UCSF and was reported at ASCO 2008. A video presentation by the major author, Johann S. de Bono, presented the combined results of treatment of 44 men with metastatic prostate cancer who had progressed *after a median of 3 prior hormone interventions*. The median baseline PSA of the men was 75 ng/mL; 31 of 44 had bone metastases, and 21/44 had measurable disease. Sixty-one men showed a >50% decline in PSA; one-half, a >75% fall; and one-quarter, a >90% decline. The overall median time to PSA progression was 252 days. Regression and healing of bone lesions were observed with one-half of men showing partial objective responses, and reduction in pain was reported.

Abiraterone has shown therapeutic usefulness for men *following chemotherapy*. Currently, chemotherapy is reserved for therapy of progressive prostate cancer after all hormonal manipulations have failed, i.e. for symptom threatening "castrate-resistant" cancer. Even after chemotherapy - successful or not - within this group there potentially are many men who would respond to an effective, additional hormone intervention - e.g. abiraterone. Expectation for success in this situation arose from the observation that in CRPC the intracellular level of CYP is many times greater than in localized cancer.

Encouraging responses to abiraterone in this setting were presented by Danila et al. at the 2008 ASCO Annual Meeting, abstract 5019: "Abiraterone acetate and prednisone in patients with progressive metastatic castrate- resistant prostate cancer (CRPC) after failure of docetaxel-based chemotherapy." Abiraterone was dosed at 1000 mg PO QD and combined with prednisone 5 mg BID. Of 35 evaluable patients treated with abiraterone, 31% progressed within 3 months, 26% within 6 months, 6% after 6 months, and 7 and 6 patients remain on treatment for 3-6 months and for 6+ months, respectively. At 3 months 40% had shown a decline in PSA >50% from baseline. The authors concluded: "Classifying these patients as hormone-refractory is a misnomer with the potential to deny patients potentially effective treatment."

An international Phase III trial is currently ongoing enrolling men with CRPC who have failed docetaxel chemotherapy. The protocol schema compares abiraterone plus prednisone to placebo plus prednisone. Details of the trial, the eligibility requirements, and the locations sponsoring the trial are available on a very informative URL: http://www.clinicaltrials.gov/ct2/show/NCT00638690?term=abiraterone&rank=3. Additional information can be found at: http://www.icr.ac.uk/press/patient_info_abi/index.shtml.

In a JCO editorial accompanying the Attard report of the Phase I trial, Raghavan and Klein comment with enthusiasm, "This study suggests that abiraterone acetate actually be *will* helpful to patients, and thus should be taken seriously as a salvage therapeutic choice."

NEW AGENTS FOR TX: DENOSUMAB - Amgen's Forthcoming Drug, An Inhibitor of Bone Resorption

On July 20th Amgen released a press report showing encouragingly positive results of a placebo-controlled 1400 man Phase 3 trial in men with non-metastatic prostate cancer undergoing androgen deprivation therapy. The study showed a significant increase in bone mineral density in the lumbar spine in men receiving denosumab, administered subcutaneously once monthly, compared to control subjects. During 36 months of observation the treated men experienced fewer than half the number of new vertebral fractures and fewer non-vertebral fractures than the placebo group. Arthralgia, back pain, constipation and pain in the extremities were the most common side effects.

Companion press reports cited two other Phase 3 placebo-controlled studies: one in which denosumab increased bone mineral density and significantly reduced the incidence of vertebral and hip fractures in women with breast cancer receiving aromatase inhibitor therapy; and a second study with similar results which evaluated 7800 women with post menopausal osteoporosis. In the latter study the drug was administered by subcutaneous injection once every six months.

FDA approval for the clinical use of denosumab awaits full evaluation of safety data. All told more than 19,000 patients participated in trials world- wide. The complete data set from the trials is expected to be presented in September to the American Society of Bone and Mineral Research.

Denosumab is a fully humanized monoclonal antibody and functions through an intricate sequence of molecular interactions to shut down the bone resorbing osteoclasts. The advantage of being constructed on a human-type immunoglobulin structure largely avoids the allergic reactions and rejection that plague antibodies built on mouse immunoglobulins.

The details of bone metabolism are complex. Osteoblastic bone building is counteracted by osteoclastic bone resorption in a finely tuned feedback regulation that underlies the constant process of bone remodeling. Although dedicated primarily to ***bone construction***, the osteoblast also participates in a feedback control loop which promotes osteoclastic ***bone resorption***, thus counterbalancing the bone buildup. The osteoblasts contribute to bone resorption by secreting a messenger, RANK Ligand (RANKL), which binds to receptors on immature osteoclasts leading to their differentiation, fusion, and transformation into mature, multinucleated, bone-resorbing osteoclasts.

But in another twist of feedback dexterity, the osteoblast also secretes osteoprotegerin (OPG) - a veritable decoy receptor to which RANKL binds. By intercepting and binding RANKL, OPG opposes

RANKL's positive effect on osteoclasts thereby ***inhibiting*** their formation. In this complex interplay, it is the ***ratio*** of RANKL and osteoprotegerin that regulates osteoclastic bone resorption.

Enter Denosumab. Denosumab, like OPG, also binds to and inactivates RANKL, and does so with high affinity and specificity. By augmenting the function of OPG, denosumab aids in pushing the RANKL/OPG ratio in favor of the OPG's suppression of osteoclastic function. The result: bone resorption is inhibited.

Denosumab will not have the field of inhibition of bone resorption to itself. Zometa (zoledronic acid), a bisphosphonate, has been available to clinicians for 10 years or so and has established a very favorable record in combating bone loss from androgen deprivation therapy, forestalling pathologic fractures and reducing bone pain in cancer patients. In one study of men with prostate cancer and a positive bone scan the use of Zometa, dosed at 4 mg every 3 weeks, reduced the occurrence of "skeletal related events (SRE)" (pathologic fractures, spinal cord compression, hypercalcemia and the need for radiotherapy for palliation of bone pain) so that 38% of the treated group experienced a SRE vs. 49% for controls. The first SRE in the Zometa group was delayed occurring at a median of 488 days from study start compared to 321 days for the placebo group. When Zometa, dosed at 5 mg every 3 months over one year, was administered to men with no evidence of bone metastases who were receiving androgen deprivation, the bone mineral density in the lumbar spine increased by 4% compared to a bone density ***loss*** of 3% in the placebo group. Even a single annual dose of 5 mg of Zometa was shown not only to reverse the approximately 5% first-year bone loss from ADT in men without bone metastases, but increase bone density in the lumbar spine by 4%. These are the Zometa statistics against which denosumab therapy will have to be compared.

Like denosumab, Zometa inhibits osteoclastic bone resorption, but accomplishes this by a different mechanism. As a bisphosphonate, a molecule containing two phosphate groups and a long side chain, it is ingested into osteoclasts but is ***non-functional*** phosphate and binds and blocks two important enzyme systems thereby impeding the formation of osteoclasts, disrupting the mechanism that allows osteoclasts to attach to the bone matrix to facilitate resorption, and effecting osteoclast apoptosis. There is some data that suggests that Zometa has a direct cytocidal effect on cancer cells.

Zometa has been in use long enough to reveal a low incidence of significant side effects: renal damage, osteonecrosis of the jaw, and more recently, spontaneous long bone and hip fractures. The subcutaneous route of administration for denosumab offers a practical advantage over Zometa, which is given intravenously over 15 minutes.

It is too early in the history of denosumab to know how it will compare in effectiveness to the serviceable Zometa, but the separate mechanisms of action of the two drugs suggests that there may be important differences in therapeutic results and side effects of the two drugs. A head-to-head comparison is ongoing in protocol #2 below

There are two clinical trials involving denosumab which are currently open to registration:

1) "Study on Prolonging Bone Metastases-Free Survival in Men With Hormone Refractory Prostate Cancer," and
2) "Double-Bind Study of Denosumab Compared With Zoledronic Acid [Zometa] in the Treatment of Bone Metastases in Men With Hormone-Refractory Prostate Cancer."

Detailed information about these trials is available at: http://www.clinicaltrials.gov/ct2/results?term=denosumab+prostate+cancer. For information about registration, details of eligibility, and study location call 1-866-5721-6436

Amgen is to be congratulated for its sustained research program in developing this new and promising drug.