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PCa Commentary

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"SPECIAL ISSUE ON XTANDI"

Xtandi (aka enzalutamide): Just The Facts, Please.

Xtandi currently is frequently prescribed, and it is likely to become even more commonly used. For that reason this article is intended to be a primer to present the basics. Paragraph headings allow the reader to skip to topic areas of interest.

1. FDA approval

Xtandi is currently approved for the treatment of men with metastatic castration resistant prostate cancer (CRPC) after chemotherapy. FDA approval for its use in CRPC prior to chemotherapy will likely occur soon based on the very favorable results of the recently reported PREVAIL trial (see below).

2. Xtandi Dosing

The recommended dose of 160 mg daily, four 40 mg capsules taken together once daily with or without food.

This dose was established in a phase 1-2 study evaluating a wide range (30 - 600 mg/day) of doses, aiming for the optimal balance between response and adverse effects (Scher H. *et al. Lancet.* April 2010).

"PSA declines were dose-dependent from 30 mg to 150 mg/day but reached a plateau between 150 and 240 mg/day above which no additional antitumor effects were seen." However, antitumor effects were seen at all dose levels.

PSA declines were seen significantly more frequently when the drug was used prior to chemotherapy. The drug's serum half-life is about one week, and after daily dosing a steady serum level is reached in about 4 weeks.

3. Mechanism of Action

Xtandi is classified as an "antiandrogen" and is significantly more potent than the currently available antiandrogen bicalutamide (Casodex). It binds the androgen receptor (AR) ligand pocket with greater avidity than Casodex and similarly blocks receptor access of testosterone (T) and dihydrotestosterone (DHT). Xtandi prevents translocation of the activated AR into the nucleus and inhibits the requisite assemblage of co-activators. The interruption of the AR nuclear translocation prevents its binding to DNA preventing gene expression of the many DNA androgen response elements.

Mechanism of Action continued:

Although the major clinical trials of Xtandi were carried out in the "castrate" setting, Xtandi *may not* require concomitant androgen suppression with an LHRH inhibitor (i.e. Lupron or Degarelix). This possibility is under active study and if validated it would represent a marked advantage of Xtandi over Zytiga (abiraterone). Used alone, Xtandi, *raises* serum testosterone (in one study to 114% over baseline) and raises serum estrogen.

Xtandi increases body fat by ~7%, reduces lean body mass by ~4%, elevates serum cholesterol by ~4-5%, and does not significantly affect serum lipid levels or alter glycemic profiles. These actions are in marked contrast to the well recognized adverse effects of suppressed T from Lupron and Degarelix.

4. Pharmacology

The metabolic degradation of the drug occurs primarily in the liver by two important enzymes in the Cytochrome P450 family, CYP 2C8 and CYP 3A4.

"Grapefruit or grapefruit juice may inhibit CYP 3A4 metabolism in the liver and intestinal wall, and theoretically may increase the plasm level of enzazlutamide, however, avoiding grapefruit or grapefruit juice does not appear to be necessary during drug treatment" (BC Cancer Agency Cancer Drug Manual, 2013).

Drug interactions: Many drugs either compete with Ztandi for metabolic degradation by these and other related enzymes (or inhibit these enzymes) and raise Xtandi blood levels. Examples of drugs that might be in common use are fentanyl, quinidine, prilosec, and coumadin. If coumadin is required, then more frequent monitoring is advised.

Urinary excretion accounts for 71% of the elimination of metabolic products and 14% is excreted in the feces. Only advanced dysfunction of the liver and kidneys would warrant dosing alteration (El-Amm *et al. Clin Med Insight Oncol.* 2013).

5. Side Effects

The major adverse effect of Xtandi is fatigue. Fatigue occurs in 30-40% of men and develops to significantly troublesome levels (grade 3/4 level) in 4 -11%. Gynecomastia is seen in 36% of men.

If a man is responding to Xtandi but is seriously affected by fatigue, based on the results of the Scher's phase 1/2 study, one option would be to withdraw the drug, wait for a period of time, and restart Xtandi at a lower dose.

Currently LabCorp does not offer testing of this enzyme, so the best approach would be to avoid taking medications that inhibit the metabolism of Xtandi. Competition for Xtandi metabolism could lead to higher than anticipated blood levels and increased adverse effects.

Other side effects include nipple pain, 19%; and hot flushes, 18%; back pain, hypertension, and occasionally joint pain.

6. Resistance

Resistance to Xtandi can be encountered *de novo* or be acquired during Xtandi therapy as a result of mutations in the androgen receptor. At the onset of treatment only about 1/3 of men respond to Xtandi due to primary resistance.

During the course of therapy 80-95% of patients acquire resistance resulting from a variety of mechanisms. Resistance can develop as early as ~6-12 months.

One example: A single missense mutation, AR F876L, substitutes a single amino acid in the ligand binding pocket and confers resistance to Xtandi by switching the drug from an antagonist to an agonist. (Nelson *et al, Cancer Discovery* 2013:3) This is similar to the antagonist-agonist switch resulting from AR mutations seen in therapy with flutamide and bicalutamide. In those situations drug withdrawal in ~30% of instances will reverse the rising PSA, i.e. the so-called "withdrawal effect." There is early evidence that a "withdrawal effect" can also occur to a yet to be determined extent upon stopping Xtandi. A practical maneuver in the face of a rising PSA after an initial PSA response might be to refrain from initiating a follow-up therapy for a time (say, a month or so) to observe if a "withdrawal effect" might occur.

A second example — Mutations leading to AR variants: Mutations have been identified that confer resistance to Xtandi by creating variants in the AR structure that bypass canonical activation of the AR ligand binding domain. This type of mechanism may be operative in as many as 80% of instances of acquired resistance. These variants entirely lack the ligand binding pockets targeted by androgens and antiandrogens (i.e, Xtandi). Instead, these AR variants bypass antiandrogen inhibition completely and continuously promote DNA transcription (Li Y, *et al. Cancer Research Jan, 2013)*.

Example three: Sawyers *et al. (Cell* Dec 2013) demonstrated that Xtandi can induce expression of the glucocorticoid receptor (GR). The GR, bound by corticosteroids, then activates the "androgen response" genes, thus entirely bypassing signaling through the AR.

Example four (rare): A switch in tumor composition from a hormonally responsive adenocarcinoma to a therapy resistant neuroendocrine phenotype can result from mutations or effectively purging the tumor of the drug sensitive adenocarcinoma.

With the increasing use of Xtandi, resistance of these sorts will become increasingly important. Mechanisms to overcome resistance will be necessary and are under active study.

7. Cross-resistance

A small study suggests "Previous abiraterone therapy is associated with a less marked fall in PSA following enzalutamide therapy in post-chemotherapy mCRPC patients … " (Thompson FB, *Scand J Urol. Nov 2013).* Prior conticosteroid usage can also diminish response to Xtandi. Yet another small study found that prior therapy with Taxotere diminishes response to both Xtandi and Zytiga (van Soest, *Eur J Cancer. 2013 Dec)* suggesting that these drugs share a common action pathway.

This raises the issue of the optimal sequencing of the newer agents, i.e. Xtandi and Zytiga, also under active study.

8. Results of 2 Major Pivotal Phase III Trials

AFFIRM trial:
This trial compared Xtandi to placebo in men with metastatic CRPC after failing Taxotere and showed a 4.8 month overall survival advantage for the drug, 18.4 v. 13.6 months, with significant improvement in other clinical endpoints. The AFFIRM trial was the basis of FDA approval for use in this setting. Abstract #6 at the 2013 GU Cancer Symposium reported that the treatment outcomes and safety profiles were similar for men ≥75 compared to men <75 years old.

PREVAIL trial:
This trial, recently reported as an abstract at the ASCO 2014 GU Symposium, will likely serve as the basis for FDA approval of the drug for use in men with CRPC showing biochemical progression having had no prior chemotherapy.

The study evaluated Xtandi v. placebo in men with asymptomatic or mildly symptomatic metastatic CRPC cancer. Androgen deprivation was continued during the trial. The trial end points were overall survival and time to radiographic progression. Between September 2010 to September 2012, 1715 men were treated.

Interim results: The objective response to Xtandi was 59%, including 20% with complete responses. The time to initiation of subsequent chemotherapy was 28 months for men on Xtandi v. 10.8 month, placebo. The Xtandi cohort experienced a 30% reduction in the risk of death and an 81% reduction in risk of radiographic progression. The median time to radiographic progression was 3.9 months for men on the placebo. That end point had not been reached in the Xtandi group by the time of the analysis.

9. Xtandi *Without* Androgen Deprivation

A small but provocative phase I/II trial, abstract 5001, was reported at the 2013 ASCO GU Conference in which 67 non-castrate men with all stages of prostate cancer were treated with Xtandi alone upon a rising PSA after primary therapy. All testosterone levels were above 230 ng/dl; median PSA was 18.2 ng/ml; and the trial duration was 6 months. The definition of response was a T level of > 80% of baseline and 92% of men exceeded this endpoint. The median PSA decline was 99.6% of baseline.

It is currently unclear how long Xtandi alone can effectively suppress AR signaling in this setting. The follow-on evaluation will reveal the timing and the extent to which resistance develops. It is entirely possible that for optimal results the addition of an LHRH inhibitor (or possibly dutasteride or abiraterone) may be necessary. Further evaluation is in progress.

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