SEATTLE PROSTATE INSTITUTE
1221 Madison St., First Floor
Seattle, WA 98104
P 206-215-2480
www.seattleprostate.com

PCa Commentary

Volume 82 July – August 2013

ZYTIGA (Abiraterone): Just the Facts, Please.

Abiraterone [AA] has now been FDA approved for use in men with metastatic castrate-resistant prostate cancer [mCRPC] prior to chemotherapy on the basis of an extensive phase III trial, COU-AA-302, (NEJM Jan 2013). Abiraterone+prednisone [AA/P] showed an 8.2 month delay (16.5 v. 8.3) in radiographic disease progression as compared to prednisone alone in men with advanced metastatic disease. Greater than 10 metastatic bone lesions were seen on bone scans in the majority of men. In this trial there was a 47% reduction in the risk of radiographic progression, and a 25% decrease in risk of death. Additionally, AA/P delayed the need for opiates and the use of chemotherapy. Later data analysis indicated an increase in median survival. AA/P dose was 1000 mg/d plus prednisone 5 mg twice daily along with continued medical or surgical castration.

Based on this evidence of benefit AA/P will likely take the pole position in the line-up of therapy for first-use in men with metastatic disease exhibiting a rise in PSA during androgen suppression. Already in competition for this initial spot is Provenge. When enzalutamide (Xtandi) is FDA approved (as is likely) for use in the same stage of disease (i.e use prior to chemotherapy), AA/P will face competition for the #1 position in treatment sequencing.

THE BASICS:

1) Why must AA/P be administered in association with castrate levels of testosterone [T]?

   In the COU-AA-302 trial the men had been either surgically castrated or were continued on a LHRH agonist (Lupron or Zoladex).

   This issue was studied by O'Donnell *et al. (British Journal of Cancer, 2004).* The biologic consequences of using AA alone, i.e. without Lupron, in men with non-castrate levels of T, i.e. >230 mg/dl, showed that although the expected drop of T (to < 50 ng/dl) was initially seen, the pituitary adjusted to the low T with rebound secretion of luteinizing hormone. The testes responded by restoring the T levels to normal. Hence the need for concomitant LHRH-R inhibition.

2) Why must prednisone be co-administered with AA?

   The consequence of AA blocking the metabolic pathway to testosterone triggers a complex feedback mechanism that clinically can lead to hypertension, elevation of blood sugar, low serum potassium, proximal muscle weakness, and fluid retention (Attard *et al, J Clin Endocrin Metab, Feb 2012).* These unwanted side-effects are lessened by prescribing prednisone at the lowest effective dose, i.e. 10 mg/d as in the COU-AA-302 trial, or even 5 mg/d, which would lessen the tendency to hyperglycemia. During AA/P treatment it is advisable to monitor blood pressure, serum potassium and glucose levels, and address fluid retention with reduction in dietary salt or a diuretic if necessary.

ZYTIGA continued:

In 15% of patients mutations can develop in the androgen receptor permitting members of the cortisol family (e.g. prednisone) to promote prostate cancer growth by signaling though the mutated AR in CRPC. (Zhao *et al., Nat Med, June 2000).* The package insert recommends monitoring liver function tests every two weeks for 3 months and monthly thereafter.

3) Are there predictors to indicate the likelihood of response to AA/P?

At the 2013 ASCO meeting Raya Leibowigtz presented an analysis of 70 men treated with AA/P at the Princess Margaret Hospital, Toronto. The response rate of those treated prior to chemotherapy was 44% compared to 33% in men treated after chemotherapy. Higher pre-treatment values (> 220U/L) for the commonly measured enzyme lactate dehydrogenase (LDH) and a ratio of blood neutrophils to lymphocytes >5, both predicted a lesser PSA response. Of note was the absence of association with response for such standard items as Gleason score, initial stage, pre-treatment alkaline phosphatase, PSA doubling time, and prior Taxotere.

Others studies have listed an elevated alkaline phosphatase, decreased serum albumin, and a poor performance rating as predictors of poor response.

Prior use of ketoconozole does not preclude a response of AA (Ryan *et al.* JCO Mar 2010), although the response rate is somewhat lower after preceding ketoconozole.

4) Does resistance to AA/P occur, and could resistance be one explanation for the termination of an initial response to AA/P?

Montgomery and colleagues from the University of Washington (Clin Cancer Res, Sept 2011) studied human CRPC tissue implanted in mice to investigate mechanisms of resistance. They reported an adaptive increase in the key enzyme (CYP17A1) with the potential to negate the initial block by AA and subvert AA's effectiveness. Another subverting adaptation was the induction of changes in the androgen receptor that permitted AR stimulation by signaling agents other than T and DHT, thereby bypassing the benefit AA's suppression of T and DHT. Corticosteroids, such as prednisone, might then function as a tumor promoter.

Considering the projected increased use of AA, resistance is likely to be seen in clinical practice. The authors speculate: "… these adaptive mechanisms can potentially be targeted by using higher dose levels of abiraterone or combinations with potent AR antagonists [such as enzalutamide] …".

A slide presentation at ASCO by Montgomery reported analysis showing a decreased response to AA/P when corticosteroids [CS] had been used <u>prior</u> to treatment with AA/P.

Their findings: prior CS usage, such as prednisone, was a prognostic factor for poorer outcome for subsequent treatment with AA/P and was associated with a 1.5 X risk of failure, i.e. an overall survival of 13.4 months for those with prior CS v. 17.3 months for those without prior CS. The authors were not contending that prior CS usage was the cause of the poorer outcome, but was instead offered as an alert that prior corticosteroids might indicate a less well population that was taking the medications to address underlying conditions that themselves could decreased response to AA/P.

ZYTIGA continued:

5) What are the adverse side effects of AA + prednisone?

A poster at the recent ASCO summarized the long-term safety of AA/P in COU-AA-302 over 30 months and found that most side effects were low grade featuring cardiac disorders, fatigue, hypertension, infection (the majority being upper respiratory and urinary tract infections), osteoporosis, and weight gain. Hyperglycemia stood out as the most prominent adverse event. Of note: the extent of adverse effects was roughly similar between men on AA+P and P+placebo.

6) Can AA+Prednisone and Provenge be given simultaneously? Does the combined use impair immunologic response to Provenge?

Initially there was concern that the immunosuppressive effects of prednisone would negate the immune response required for benefit from Provenge. At ASCO Eric Small *et al* offered a poster summarizing the results of a randomized, phase 2 trial of Provenge with concurrent or sequential AA/P in mCRPC.

Their findings: the immune response to Provenge was not impaired when given together and there was no increase in side effects from the combination.

7) Can AA/P be combined with Zometa or Denosumab in men with mCRPC?

These drugs may be safely combined and the combination can delay the advancement of bone lesions. In an ASCO poster Saad *et al.* presented an analysis of the COU-AA-302 data set (the majority of whom had bone metastases) and compared those taking a bone-targeted therapy [BTT] v. none. At a median follow-up of 27 months, the men taking AA/P + BTT delayed radiographic progression to a median of 13.6 months v. 11 months for those not taking a BTT.

Their findings: "… concomitant BTT use was associated with delayed symptomatic progression in asymptomatic and mildly symptomatic mCRPC patients." (The data did not support a comparison of AA/P + BTT v BTT alone.)

8) Does early worsening of the bone scan after AA/P indicate a lack of response to the therapy?

It is very important to note that the technetium and F-18 PET/CT bone scans are essentially metabolic studies and are "positive" as a result of detecting increased bone turnover. There can be a paradoxical worsening in a scan resulting from the process bone regeneration associated with tumor regression. This was studied by Ryan *et al.*,"Phase II Study of Abiraterone Acetate in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Displaying Bone Flare Discordant with Serologic Response (*Clin Can Res,* July 2011).

Their findings: Although 22 of 33 (67%) of men showed a > 50% PSA decline at week 12, worsening in the bone scan was seen in 12 (52%) during the first 6 months of follow-up. However, "11 of 12 subsequently showed improvement or stability." An early judgment of AA/P failure on the basis of an initial worsening bone scan (in the absence of other indcators of progression) is clearly premature.

BOTTOM LINE: Zytiga (abiraterone) is likely to be increasingly administered and used early in the sequence of available therapies for men with metastatic disease with relapsing PSA values during androgen suppression. This mental tool kit for Zytiga usage may be helpful to clinicians as they increasingly prescribe this drug.

Xtandi (enzalutamide): Moving Up Front -- A Game Changer

At the recent ASCO meeting, abstract #5001 (Smith et al.) sounds an early bell for the opening of a new era in hormone therapy for prostate cancer: "Efficacy and safety of enzalutamide (ENZA) monotherapy in hormone-naive prostate cancer (HNPC)," i.e., prior to androgen deprivation.

Xtandi currently is FDA approved for use in mCRPC after chemotherapy, while Zytiga is approved for use in mCRPC prior to chemotherapy. Xtandi has shown the potential to function independent of androgen suppression by LHRH-R inhibition. If Xtandi alone were found effective in mCRPC, or even "way up front," as used in the Smith study, the adverse effects of androgen suppression could be avoided.

Research is currently only in the early stages of exploration of the roles of enzalutamide (alone or in combination) and of abiraterone (alone or in combination) in localized prostate cancer. For example, the results from ongoing study, NCT01547299, will indicate the comparative effective of enzalutamide v. enzalutamide/leuprolide/dutasteride in localized prostate cancer prior to prostatectomy.

The FDA approval of Xtandi in men with metastatic CRPC following docetaxel (Taxotere) chemotherapy was based on the phase III trial showing a 5 month increase in overall survival for enzalutamide v. placebo in men with this stage of disease. The very favorable results of Smith's small study (see below) makes Xtandi a promising candidate for first-line therapy for a PSA rise following primary therapy, i.e after surgery or radiation but prior to androgen suppression. To be secure in that first-line role, the results of this study and others will have to be validated, particularly comparing the duration of PSA control to standard LHRH-R inhibitors, (i.e Lupron or Fermagon).

The placement of an anti-androgen such as Xtandi as the first line of defense for PSA relapses after primary therapy is not unprecedented. In 2010 Iverson et al. (BJU Int, Apr) reported the final results at 9.7 years of follow-up of a study of 150 mg bicalutamide (Casodex) v. placebo. They reported a benefit from bicalutamide in terms of progression-free survival for men with locally advanced (but not men with localized disease) and an overall survival benefit for 150 bicalutamide in men relapsing after radiotherapy. In their opinion this therapy "might represent an alternative for patients with locally advanced disease," especially those wishing to preserve quality of life as compared to treatment with an LHRH-R agonist. In current studies enzalutamide is replacing bicalutamide.

Enzalutamide interrupts the growth-promoting activity of the androgen receptor within the prostate cancer cell in three ways: it blocks the access of DHT to the androgen receptor (AR) blinding clef; inhibits the transport of the AR to the cell's nucleus; and interrupts the assembly of cofactors necessary for AR binding to AR response elements on the DNA. Bicalutamide, enzalutamide's weaker brother, is considerably less efficient in performing these functions as it binds to the AR with much less affinity.

Smith's abstract in detail:

In Smith's small phase II study 67 men, mean age 73 years, were treated with enzalutamide (160 mg/d) and evaluated at 25 weeks. Of this group 39% had metastases, and 60% had tumor stage T0-T2. Twenty four percent had prior radiotherapy or surgery. Having had no prior hormone therapy, their median serum testosterone was normal, > 230mg/dl. The median PSA of the men was 18.2 ng/ml; half had Gleason score 7, and a quarter ≥Gleason 8.

Xtandi continued:

The Findings:

1) 92% percent of men both with and without metastases showed PSA declines of ≥ 90% from baseline values achieving PSA values of ≤ 4 ng/ml at 6 months. The median PSA decline was 99.6%. In the group free of metastases half dropped to a PSA level of ≤ 0.1 ng/ml whereas in the metastatic group 40% achieved that level.

2) Among those men evaluable, objective responses were seen in 50%;

3) Bone mineral density was essentially stable decreasing only 0.24%. [Lupron decreases bone density by ~5% at one year];

4) Total cholesterol increased only 4.55% and triglycerides by 6.48%;

5) Markers for diabetes did not increase, but instead stayed essentially stable: hemoglobin A1c declined by ~2% and fasting glucose was lowered by .1% [This is in marked contrast to substantial elevations of both with Lupron therapy];

6) Consistent with the expected effect of anti-androgens on serum hormone levels, *serum* testosterone levels *increased* 114%. [The dichotomy of anti-androgens maintaining or increasing serum T levels while lowering intraprostatic DHT levels is the key to understanding the contrasting biologic effects of anti-androgens v. LHRH-R agonists and antagonists.]

In comparison to the well recognized toxicity of agents that lower serum testosterone (Lupron, Firmagon, Zoledex) the adverse effects of enzalutamide were mostly low-grade in severity: gynecomastia occurred in 36%; fatigue in 34%; nipple pain,19%; and hot flushes in 18% of men.

BOTTOM LINE: Smith's encouraging data is based on only a small phase II study and needs validation in a randomized trials comparing first-line enzalutamide with a LHRH-R inhibitor. However, the efficacy and safety demonstrated by enzalutamide in this up-front role, if confirmed, likely heralds the beginning of a new era in the hormone management of prostate cancer.

Provenge: Benefit Increases When Used at Lower Baseline PSA Values

It is perhaps understandable to minimize the importance of the 4.3 month median extension of survival recorded in the IMPACT trial of Provenge v. placebo for men with metastatic CRPC, especially considering the list price of $93,000 for three administrations. However, a recent re-analysis of the study data reported by Shellhammer, Kantoff *et al.*, (UROLOGY, 2013, Apr) is likely to modify that opinion and move Provenge (along with Zytiga) to a front-line position in consideration of treatment of men early in the course of metastatic CRPC.

The conclusion of the Shellhammer article is indicated in its title: "Lower Baseline Prostate-specific Antigen Is Associated With a Greater Overall Survival Benefit from Sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) Trial. The analysis' objective was "to explore the prognostic and predictive value of baseline variables in 512 patient with metastatic castrate-resistant prostate cancer … ." The IMPACT trial studied asymptomatic, or minimally symptomatic, men with any Gleason score and PSA ≥ 5 ng/ml.

Provenge continued:

Their findings: A patient's baseline PSA value was the strongest predictor for benefit from Provenge treatment (p=<0001). As baseline PSA increased, overall survival [OS] decreased.

PSA values were segregated into four quartiles (≤ 22.1 ng/ml; >22.1 - 50.1; >50.1 - 134.1; >134.1). Median OS progressively decreased from 41.3 months to 27.1 , to 20.4 , and to 18.4 months respectively in those subgroups. These median OS figures represent a benefit for Provenge therapy over placebo of 13 months, 7, 5.4 and 2.8 months in the four quartile.

Other standard variables prognostic for overall survival, i.e., lactic dehydrogenase (LHD), and alkaline phosphatase (ALP), Gleason score, and ECOG performance status, were also significant for survival (p <.05). Men with lower values for LDH (another surrogate for tumor burden) and better performances status "experienced longer survival and greater benefit from" Provenge. For those men with bone-only disease, a lower ALP appeared to confer greater benefit.

By employing the PSA level as a surrogate for the extent of tumor burden, the study confirms the prevalent concept that immunotherapy is most effective when pitted against the least amount of cancer. Unlike chemotherapy, sufficient time is required for the immune system to be effectively activated. Tumors themselves are immunosuppressive, so that a minimal burden offers the least inhibition of the host's immune response. Clearly, the take-home advice is when using Provenge prescribe it early in the development of mCRPC.

BOTTOM LINE: The authors' conclusion: "… the greatest magnitude of benefit with sipuleucel-T was observed among patients with better prognostic factors and particularly those with lower baseline PSA values."

Ed Weber, M.D.
Editor

"I want to thank Dawn Scott, Staffperson, Seattle Prostate Institute, and Mike Scully, Librarian, Swedish Medical Center for their unfailing, timely, and resourceful support of the Commentary project. Without their help this Commentary would not be possible."