

Quality of Life and the mCRPC Patient

HISTORY OF PROSTATE CANCER: DIAGNOSIS AND TREATMENT TIMELINE, 1904 TO 2012

- 1904 Radical perineal prostatectomy (Hugh Hampton Young)
- 1913 Direct implantation of radium into prostate
- 1936 Elevated acid phosphatase in PCa (Ethel and Alexander Gutman)
- 1941 Beneficial effects of castration and estrogen in men with advanced PCa (Charles Huggins)
- 1947 Retropubic radical prostatectomy (Terrence Millin)
- 1962 Megavoltage radiation for localized PCa (Malcolm Bagshaw)
- 1966 Gleason scoring developed
- 1973 National Veterans study reports benefits of hormonal therapy
- 1975 First RTC using chemotherapy in prostate cancer (W.W. Scott, et al.)
- 1980 PSA found elevated in serum of men with prostate cancer
- 1981 LHRH analogues first used
- 1983 Nerve-sparing prostatectomy preserves erectile function (Patrick Walsh)
Transperineal implantation of radioactive seeds (H. Holms)
- 1985 FDA approves Leuprolide® to treat PCa
- 1986 FDA approves PSA to monitor PCa
- 1987 Researchers identify new specific sub-set of prostate tumors (neuroendocrine, also called small-cell tumors that grow and react to treatment differently than to the common form of PCa adenocarcinomas)
- 1988 Ultrasound guided biopsy device approved
- 1989 FDA approves antiandrogen flutamide
- 1990 Watchful waiting (active surveillance) introduced to avoid unnecessary radical treatments 3-D conformal radiation therapy developed
- 1994 FDA approves PSA for screening to detect early PCa
- 1995 Meta-analysis trial of androgen blockade concludes no significant benefit from combining these drugs
- 1996 FDA approves anthracenedione Novantrone® to treat advanced prostate cancers that do not respond to hormone therapy
- 1997 Combination of radiation and hormone therapy to improve PCa survival become standard
- 2003 Two large clinical trials report Proscar® and Avodart® reduce the risk of developing prostate cancer by up to 25 percent
- 2004 FDA approves antimicrotubule agent Taxotere® for hard-to-treat prostate cancers
- 2008 FDA approves CellSearch®, a test for predicting survival and monitoring the impact of treatment for men with advanced prostate cancer
- 2009 Radiation after surgery or hormone therapy improves survival
Clinical trial reports adjuvant radiation reduces risk PCa will spread
- 2010 FDA approves autologous cellular immunotherapy Provenge® for advanced prostate cancer
FDA approves anti-microtubule agent Jevtana® given with prednisone for advanced prostate cancer that progressed despite prior hormone therapy and chemotherapy with docetaxel
- 2011 FDA approves the anti-androgen Zytiga® in combination with prednisone for treatment of advanced prostate cancers whose disease progresses despite prior hormone therapy and standard chemotherapy with docetaxel
- 2012 FDA approves anti-androgen Xtandi® for late stage cancer

REFERENCES

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- http://www.cancerprogress.net/downloads/timelines/progress_against_prostate_cancer_timeline.pdf
- <http://www.empr.com/fda-approved-prostate-cancer-drug-treatments/article/123619/#>
- <http://www.fda.gov>

THE ART AND SCIENCE OF MEDICINE: ADVANCED TREATMENT FOR PROSTATE CANCER

Published on December 11, 2012

An interview with Deepak A. Kapoor, MD, president of LUGPA, and chairman/CEO of Integrated Medical Professionals.



Deepak A. Kapoor, MD, President, Large Urology Group Practice Association (LUGPA); Chairman and CEO, Integrated Medical Professionals, PLLC; President, Advanced Urology Centers of New York (a division of Integrated Medical Professionals and the largest urology group practice in the United States); Chairman, Access to Integrated Cancer Care (an informal advocacy group representing the rights of patients to access integrated services); Chairman, SCRUBS RRG; and member, Board of Directors of Allied Urological Services (the largest lithotripsy partnership in the U.S., and serves as Chairman of the Finance Committee).

During the Large Urology Group Practice Association (LUGPA) annual meeting in November, an unprecedented number of urologists arrived one day early to attend a CME course focusing on how large-group urology practices can integrate and incorporate the new prostate cancer drug therapies for the treatment of advanced prostate cancer. Deepak A. Kapoor, MD, President of LUGPA, said, "Currently, nationally, we lack a standardized approach for the treatment of advanced prostate cancer, but this is an exciting time when, as urologists, we have new treatment options for the mCRPC patient that are less toxic, have fewer side effects, and are demonstrating an improvement in the patient's quality of life."

The LUGPA prostate cancer session brought together a panel of thought leaders and specialists in surgical urology and oncology, including Paul Lang, Judd Moul, David Crawford, and Neal Shore, discussing how to deliver these therapies in a large group setting.

"Most urologists are very comfortable with localized therapies for prostate cancer; however, the newer modalities of treatments for CRPC are really challenging urologists because historically, once the patient becomes refractory, that patient is typically referred to the medical oncologist," said Dr. Kapoor. "Most urologists don't offer infusion therapies and are not prepared to manage the whole range of complications."

How is this time pivotal?

Now, with a new spectrum of drugs, some being offered earlier in the treatment cycle, Dr. Kapoor says it's an exciting time to manage these patients because we have options now besides chemotherapy. He suggests, "integrating these new drugs into practice involves a fundamental change. Urologists are well positioned, with their expertise, to manage the CRPC patient because they know this patient (often for 10 years or more) through active surveillance of the disease. The patients, in turn, are very comfortable with their urologists managing the care, creating the team, and quarterbacking the treatment regimen."

Is the large group urology practice adaptable to these novel therapies?

"Many large group practices, like ours, are conveniently located to the patient, improving access of care. We work in the patients' neighborhoods and collaborate with the medical oncologist to form a treatment team." Integrated Medical Professionals is the largest urology group practice in the U.S., with more than 100 physicians in six clinic locations. Each of these clinics is within a seven-mile radius of one another in the NYC/Long Island area.

Would a standardized treatment paradigm benefit from one definition for CRPC?

"This is a very important question. For the CRPC patient, we (as urologists) lack a standardized approach, nationally, to looking at the disease. Similarly, there is frustration among some of the urologic-oncology frontrunners involved in the clinical trials—asking why more patients aren't getting access to these new novel therapies. We need to have more discussions within our groups and at association meetings on how to initiate a bone scan, or what is the appropriate PSA doubling time, or how to quantify the radionuclear modalities for detecting metastatic prostate disease and recognizing the role of CT and MRI. It also includes asking the group practice to be proactive by fine-tuning the active surveillance protocol with respect to the new drug therapies."

What are the triggers when you select patients for these new treatments?

"We now have something to offer the CRPC patient besides chemo, and as result are paying more attention to profiling the patients who are well-suited for the new treatments. Urologists are one of the more pragmatic specialists in medicine. We focus on evidence-based medicine, but we also need to address real questions that can apply to real solutions for real patients. These drugs are no longer theoretical concepts. Ultimately the risk/benefit ratio applies, but it's a challenge in these economic, cliffhanging times. As physicians and researchers, we are in

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the evolution of many great advances in the targeted delivery of medicine, yet our resources to treat the patients are really becoming very restrained. I believe urologists, especially those in multidisciplinary organizations, will continue to move the treatment paradigm forward and embrace the knowledge, improve the access to care, enhance the outcomes of our cancer patients with a higher level of quality of life, while decreasing costs."

So how can urologists bolster the CRPC patient as new therapies are approved?

"So much of what we (as urologists) focus on is the science of medicine, the evidence and facts that command decision-making, and patient management. In my experience, the patient hears the technical facts, but those facts don't help the man feel in control of the cancer-fighting process. Often the facts frighten the patient even more." Dr. Kapoor refers to "high quality care delivery" as the foundation for every urology practice (it's expected), but what makes the difference is an integrated and personalized urology-driven team approach. "The team needs to be sensitive to the patient's fears and apprehensions and provide the man and his family with resources to foster a positive treatment experience."

"Within LUGPA, we talk about providing a neighborly interaction that reflects the patient's community," says Dr. Kapoor. "Large urology group practices are often urologic cancer centers that are community centric and bring tertiary



care to where the patient lives. I say this often. if you improve access, you will improve outcomes and reduce costs."

About LUGPA: LUGPA represents 115 large urology group practices in the United States, with nearly 2,000 physicians who make up more than 20 percent of the nation's practicing urologists. LUGPA and its member practices are committed to best practices, research, data collection, and benchmarking to promote quality clinical outcomes. For more information, visit www.lugpa.org.

Written by Karen Roberts, Medical Editor, UroToday.com

THE IMPACT OF ABIRATERONE ACETATE THERAPY ON PATIENT-REPORTED PAIN AND FUNCTIONAL STATUS IN CHEMOTHERAPY-NAIVE PATIENTS WITH PROGRESSIVE, METASTATIC CASTRATION-RESISTANT PROSTATE CANCER - LECTURE PRESENTATION

Published on November 15, 2012

This presentation is part of an ongoing interactive case-lecture series: Advances in Treating Metastatic Castration-Resistant Prostate Cancer available at http://www.urotoday.com/index.php?option=com_content&Itemid=831&catid=1341&id=55386&lang=en&view=article.



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UroToday presents the second title in a multi-part, online, interactive case-lecture series entitled, "Advances in Treating Metastatic Castration Resistant Prostate Cancer." In this presentation, Dr. Charles Ryan discusses quality-of-life results, demonstrating a more real-world view of how patients actually feel and function when receiving abiraterone acetate therapy.

Charles J. Ryan, MD, is an Associate Professor of Medicine in the Division of Hematology / Oncology at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco (UCSF) where he is the leader of the Genitourinary Medical Oncology Program. He received his MD from the University of Wisconsin in Madison and completed his residency in internal medicine at the University of Wisconsin Hospital and Clinics, where he also served as Chief Resident. He completed a fellowship in medical oncology in the Department of Medicine at Memorial Sloan-Kettering Cancer Center and the Joan and Sanford I. Weill Medical College of Cornell University in New York.

His clinical and research work centers on the design and conduct of clinical trials of novel therapies for advanced prostate cancer, specifically secondary hormonal therapies targeting adrenal androgen signaling, insulin growth factor inhibitors, androgen receptor targeted therapy and chemotherapy. In addition to clinical trials, Dr. Ryan collaborates with many laboratories researching the role of the androgen receptor and other signaling mechanisms in prostate cancer patients.

Dr. Ryan is a member of several honor societies and is the recipient of a Leadership and Service Award and the John Kimberly Curtis Award from the University of Wisconsin Medical School. He received the American College of Physicians/

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American Society of Internal Medicine Evergreen Award in 2000 and the American Society of Clinical Oncology Merit Award and Cancer and Leukemia Group B: Young Investigator Award, both in 2003. He was awarded the Donald Coffey Career Development Award from the Prostate Cancer Foundation in 2006 and a California Coalition to Cure Prostate Cancer Award in 2007.

AN INTERVIEW WITH CHARLES J. RYAN, MD: PRESENTATION OF THE NEW PARADIGMS FOR HORMONE THERAPY IN PROSTATE CANCER

Published on June 21, 2012

Perspectives on the interim analysis results of COU-AA-302 were discussed with Charles J. Ryan, MD, in this exclusive interview with UroToday following the prostate cancer symposium at the ASCO 2012 annual meeting.

Translating the clinical results observed from prespecified interim analyses of the randomized, placebo-controlled phase III study, COU-AA-302 demonstrated that patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate plus prednisone showed a statistically significant improvement in radiographic progression-free survival (rPFS), and all secondary endpoints, compared to patients treated with placebo plus prednisone.

UroToday: Can you provide perspective on the clinical relevance of the results observed from pre-specified interim analyses of the randomized, placebo-controlled phase III study where COU-AA-302, demonstrated that patients with metastatic castration-resistant prostate cancer (mCRPC), treated with abiraterone acetate plus prednisone, showed a statistically significant improvement in radiographic progression-free survival (rPFS) and all secondary endpoints compared to patients treated with placebo plus prednisone?

Dr. Ryan: "The first point is that anybody treating prostate cancer realizes that the application of chemotherapy in this disease is somewhat limited either by patient or physician choice due to the toxicity of that treatment. So the development of abiraterone acetate, as well as other therapies, is moving along the lines of developing oral, well-tolerated treatments that can delay progression and improve survival and that can help maintain the general well-being of patients who have metastatic castration resistant prostate cancer (mCRPC)—many of whom are free of symptoms of the disease for a long period of time. In the context of oncology in general at this time, abiraterone acetate is emblematic of where we are going as oncologists in the big picture in terms of developing more targeted, better-tolerated oral therapies.

The second point is that prostate cancer in general is getting very complicated from the standpoint of the wide variety of treatments that are becoming available and determining

where to sequence them in the spectrum of the disease.

So it is important as we talk about these results to know exactly who the patients were who were treated and what the results showed.

The third point is this phase III trial utilized co-primary endpoints, which were utilized for the reason that many of these patients have a fairly long expected survival. Therefore, only measuring overall survival as an endpoint of the trial can be complicated or contaminated by many other treatments that these patients could receive.

In light of that we used radiographic progression-free survival (rPFS) and overall survival (OS) as co-primary endpoints. The results of the study show that patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate plus prednisone, when compared to prednisone alone, led to a statistically significant and clinically meaningful delay in disease progression. By clinically meaningful, I mean it more than doubled the time until patient disease progressed compared for the patients in the abiraterone acetate plus prednisone arm to those receiving prednisone alone.

For the purposes of this study, a rising PSA did not constitute progression of the disease. What constituted disease progression was the development of new metastatic lesions. And it is important to note that in this study the average PSA was 45 and about 50% of the patients had >10 bone metastases at study enrollment. This is the first randomized study to demonstrate a radiographic progression-free survival benefit and a strong trend for overall survival in this patient population.

The fourth point is that in addition to looking at rPFS and overall survival, we looked at a series of other clinically relevant endpoints:

- Median time to opiate use for cancer pain: The median time in the abiraterone acetate plus prednisone arm was not reached and was 23.7 months in the control arm (HR = 0.69; 95% CI: [0.57, 0.83]; p = 0.0001).
- Median time to initiation of cytotoxic chemotherapy for prostate cancer: 25.2 months for the abiraterone acetate plus prednisone arm vs. 16.8 months for the control arm (HR = 0.58 [95% CI: 0.49, 0.69]; p < 0.0001).
- Median time to decline in performance status: 12.3 months for the abiraterone acetate plus prednisone arm vs. 10.9 months for the control arm (HR = 0.82; 95% CI: [0.71, 0.94]; p = 0.0053) for an increase in the Eastern Cooperative Oncology Group (ECOG) performance score of one point or more. The ECOG performance score is a standard measure used to assess functional status of a patient and is often



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used to determine prognosis and appropriate treatment.

- Median time to PSA progression: 11.1 months for the abiraterone acetate plus prednisone arm vs. 5.6 months for the control arm (HR = 0.49; 95% CI: [0.42, 0.57], $p < 0.0001$), based on The Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.

On every one of these secondary endpoints, patients receiving abiraterone acetate plus prednisone had a statistically significant prolongation on average until that event occurred. So, in summary, these results show that patients:

- can live longer without disease progression,
- can live longer without symptoms,
- can live longer until performance status deteriorates,
- can live longer until receiving chemotherapy,
- and probably live longer overall.

The overall survival results of this trial are continuing to mature. And at the time of this interim analysis, we saw a strong trend in favor of abiraterone acetate plus prednisone arm compared to the prednisone arm ($p = 0.0097$). This is an important study with all clinically relevant endpoints favoring treatment with abiraterone acetate plus prednisone, and is also the first to suggest that inhibiting androgen production significantly delays initiation of chemotherapy. There will be subsequent analysis for survival before the true statistical difference between the arms is known."

UroToday: Can you clarify the results of overall survival in this study and what may be analyzed in the future?

Dr. Ryan: "The study is unblinded and ongoing. These are planned interim analyses. The reason you do interim analyses is you are looking for an imbalance that would tell you that it is unethical to continue treating patients with placebo. These trials are monitored by Independent Data Monitoring Committees (IDMC) who do not work for the sponsor and who are not investigators on the trial. These committees are truly independent.

When the Independent Data Monitoring Committee (IDMC) looked at the data, they looked at the survival trend, they looked at this long rPFS difference, they looked at all the secondary endpoints we just reviewed. Then, they said as a group, unanimously including their statisticians, that these data demonstrate compelling evidence for clinical benefit associated with abiraterone acetate, and therefore they recommended to the sponsor that the study be unblinded and the sponsor, Janssen Research & Development, LLC, unblinded the study.

The study was unblinded in February 2012. The next interim analysis will be happening relatively shortly. We do not know yet how many patients were unblinded and crossed over abiraterone acetate. We look forward to the next interim

analysis in the near future."

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LARGE UROLOGY GROUP PRACTICE MANAGEMENT: REFLECTIONS DURING PROSTATE CANCER AWARENESS MONTH

Published on September 17, 2012

A UroToday interview with Terry FritzPatrick, Administrator, Oregon Urology Institute, September, 2012, by Karen Roberts, medical reporter.



In 2004, Oregon Urology Institute (OUI) united the expertise, reputations, and resources of two of the Northwest's leading urology practices to create a single, state-of-the-art center. By 2006, these Oregon urologists in the Eugene-Springfield area were evolving into an integrated multi-disciplinary organization. When management consultants were touting the "Centers for Excellence," this 16 physician, large group practice listened and then personalized those tenets—striving to bring together a "think tank of progressive, experienced specialists, trained in the newest treatments all under one roof." The transformation started with an outpatient surgical center. The other tenet to success was opening the channels of communication between the urologist, the oncologist, the pathologist, and the patient.

"The relationship we developed with a local pathologist and his laboratory was very important—this lab specializes in prostate cancer. The OUI urologists raised their level of interactive discussions with the pathologist. Today, after four years, we can really see the positive difference this relationship has made to the entire spectrum of care." Then came the OUI Radiation Center, the only facility in Oregon focused exclusively on prostate cancer, offering tailored IGRT treatments for prostate disease. "Then when the local hospital added robotic surgery, we attracted new physicians and technicians specializing in these minimally invasive but highly effective procedures. Having all of these services onsite is a time-saver for patients, and there is a greater sense of compliance to follow the treatment plan." Today this model is still evolving. "What we didn't anticipate was the advent of the new bone health medication treatments expected to come out this year and next." On their watch list are the new androgen deprivation therapy drugs (enzalutamide and ZYTIGA®) and the development of new immunotherapies involving interferons.

Another growth area at OUI is our urodynamic services and our full-spectrum approach to managing LUTS, overactive bladder,

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urge incontinence, and stress incontinence, especially in women. The addition of an onsite physical therapist enhances the rehabilitative needs of the patient. The psychosocial issues are largely addressed through a variety of cancer support groups that meet monthly. "These are as much for the wife as they are for the husband with prostate cancer; she asks the questions that are hard to get answers to at home." In early September OUI patients enjoyed a Survivors' Banquet—"It was a big dinner and well attended." For Fathers's Day, OUI sponsored the Prost 8K/5k Walk and had 336 participants. In July OUI hosted a free PSA screening event with local TV partners at the Eugene-area mall—"One thousand men were screened; I believe it's one of the largest in the U.S."

So how does OUI address the PSA controversy? This group has a three-point policy. "Screening is important. Get screened every year. Know your PSA number and your baseline." Of the 1,000 men screened in July, approximately 10% were asked to come into the Institute for follow-up testing, and of that number, several were scheduled for surgical procedures due to more advanced prostate cancer. "It's not a macroenvironment we live in, these are our neighbors."

"While dedicating the month of September to prostate cancer is important," says FritzPatrick, "awareness needs to happen at many other times during the year, just like it does with breast cancer awareness, and the lesser-known cancers, bladder and renal, need attention too."

So, is bigger better? "There was certainly a risk, but our physicians understood that risk and were willing to evolve and take one step at a time. We did the important things—improve how we communicate with each other and our patients and add the newest proven technologies to better diagnose and treat all types of urologic cancers and conditions. That's the kind of culture we have here at Oregon Urology."

TREATMENT OF CHEMOTHERAPY-NAIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER - CASE LECTURE PRESENTATION

Published on September 17, 2012

This presentation is part of an ongoing interactive case-lecture series: Advances in Treating Metastatic Castration Resistant Prostate Cancer located at http://www.urotoday.com/index.php?option=com_content&Itemid=831&catid=1341&id=55658&lang=en&view=article.

Bryan A. Mehlhaff, MD
Urologic Oncology, Adult & Pediatric Urology
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UroToday presents a new title in a multi-part, online, interactive case-lecture series entitled, "Advances in Treating Metastatic Castration Resistant Prostate Cancer." In this presentation, Bryan Mehlhaff, MD, of the Oregon Urology Institute, discusses the treatment history of a 49-year-old prostate cancer patient from the time of diagnosis through 2012.

An award-winning scholar and medical student while training at New York's Albany Medical Center Hospital, Dr. Mehlhaff has maintained his drive for excellence throughout his career. He honed his skills in adult and pediatric urology, endourology, and minimally invasive surgery as an assistant urology professor before entering private practice at Oregon Urology Institute. Dr. Mehlhaff continues to be at the forefront of education by serving on a urologic medical advisory board.

ANDROGEN BIOSYNTHESIS INHIBITION AND METASTATIC CASTRATION-RESISTANT PROSTATE CANCER - EXCLUSIVE INTERVIEW

Published on May 22, 2012

Judd W. Moul, MD, FACS, is the James H. Seamans, MD, Professor of Surgery and Director of the Duke Prostate Center, Duke Cancer Institute and Division of Urology at the Duke University Medical Center, Durham, NC. Prior to joining Duke, Dr. Moul was the professor of surgery at USUHS



in Bethesda, MD, an attending urologic oncologist at the Walter Reed Army Medical Center, and a former director at the Center for Prostate Disease Research. Dr. Moul currently serves on the editorial boards of Prostate Cancer and Prostatic Diseases, Prostate Cancer, BJU International, American Journal of Men's Health, Brazilian Journal of Urology, and World Journal of Urology. He has authored over 500 medical and scientific manuscripts and book chapters and lectured at U.S. and International meetings.

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At this year's American Urological Association (AUA) Annual Meeting in Atlanta, Dr. Judd Moul presented a practice management perspective on the burden of metastatic castrate-resistant prostate cancer (mCRPC), the mechanism of action for ZYTIGA® (abiraterone acetate), as well as phase III AUA Clinical Theater presentation.

Background: In mCRPC, prostate tumor cells remain androgen-sensitive by several mechanisms and the new terminology of mCRPC aptly reflects the evidence that in mCRPC the tumor remains hormone sensitive. Abiraterone inhibits the CYP17 enzyme complex required for androgen biosynthesis in the testicular, adrenal, and prostatic tumor tissue.

UroToday: What are the key points clinicians should consider when using abiraterone acetate for the treatment metastatic castration-resistant prostate cancer (mCRPC) following treatment by docetaxel with prednisone?

Dr. Moul: "As physicians use abiraterone acetate (market name ZYTIGA®) a couple of key points come up: How do you sequence this drug? At the current time, this drug is to be used after a patient has progressed on docetaxel- (Taxotere®) based chemotherapy. Then the question would come up, you start ZYTIGA® and the patient has responded, how do you know when to discontinue this drug?"

It's important to point out for the clinician, In the clinical trial where ZYTIGA® was FDA approved, the trial did not base the discontinuation on PSA alone. The patients had to have met three criteria for disease progression before abiraterone acetate was stopped. First, they had to have a 25% increase in their PSA levels over baseline when they started the drug. Second, they had to have radiographic progression (bone scan, CT scan or MRI had to show worsening of the disease). Third, they had to have symptomatic or clinical progression as defined by the physician.

From a urology standpoint we certainly know patients follow their PSA. We follow PSA and rely on PSA; however, we encourage doctors using this drug not to simply stop the drug solely based on PSA progression as well as educating our patients about how to define success and progression with this product.

In summary, key take-away messages about abiraterone acetate are:

- Abiraterone acetate inhibits CYP17, an enzyme complex needed for androgen biosynthesis, and when used in combination with prednisone improved the overall survival in patients with mCRPC who received prior chemotherapy containing docetaxel.
- In the latest analysis of the clinical trial, there was a 4.6 month survival difference comparing ZYTIGA® to

prednisone alone. That is quite impressive considering these patients had all progressed after docetaxel. This is a very advanced, difficult patient population, yet ZYTIGA® was improving the median survival by 4.6 months.

- The safety profile (for abiraterone acetate) is quite tolerable and quite good. From a testing standpoint and a clinical management standpoint (during CYP17 inhibition, since the cortisol production is blocked) there is the potential for this drug to drive this pathway toward mineralocorticoid excess.
- From a board exam and clinical management perspective, this drug can sometimes cause hypokalemia (low potassium), hypertension, or fluid retention. These are the three key side effects considered potentially unique based on the drug's mechanism of action."

This event was sponsored by Janssen Biotech, Inc. as a non-accredited AUA 2012 promotional activity.

Interviewed by Karen Roberts, UroToday medical reporter, at the American Urological Association (AUA) Annual Meeting-May 19 - 23, 2012 - Georgia World Congress Center - Atlanta, GA USA

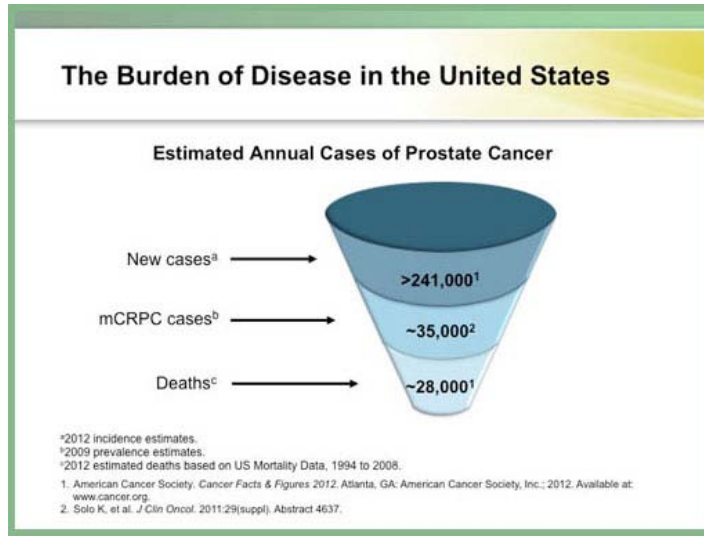
MCRPC IN FOCUS: ANDROGEN BIOSYNTHESIS INHIBITION AND METASTATIC CASTRATION-RESISTANT PROSTATE CANCER, CLINICAL INSIGHTS FROM THE CLINICAL INDUSTRY THEATER PRESENTATION BY JUDD MOUL, MD

Published on November 26, 2012

Presented by Judd Moul, MD, at the American Urological Association (AUA) Annual Meeting - May 19 - 23, 2012 - Georgia World Congress Center - Atlanta, GA USA*

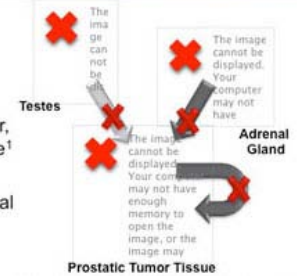
The burden of prostate cancer in the U.S. and Europe remains significant despite the fact that overall mortality has improved. Prostate cancer remains the second leading cause of cancer death in men.

This is an exciting era for new prostate cancer treatments, and specifically metastatic castrate-resistant prostate cancer (mCRPC). The estimated number of new prostate cancer cases is 241,000 and 28,000 deaths (based on ACS 2012 Cancer Facts 2012 cancer incidence) [1]. Annually, there are an estimated 35,000 mCRPC cases in the U.S. [2]. Androgen-sensitive prostate cancer responds to therapies that decrease androgen levels [3]. Androgen deprivation therapy using gonadotropin-releasing hormone (GnRH) analogs (or orchiectomy) with or without an antiandrogen is the standard approach in early disease [3,4]. The GnRH analogs affect androgen production only in the testes [3]. In eugonadal men, 90% of androgens are synthesized in the testes, 10% in the adrenals [5].



Abiraterone Inhibits Androgen Production at 3 Sites

- Abiraterone acetate is converted *in vivo* to abiraterone¹
- Abiraterone inhibits the CYP17 enzyme complex required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissue¹
- GnRH analogs do not inhibit androgen production by the adrenal glands or by the tumor tissue¹



Note: Patients in the abiraterone acetate clinical trial were using a GnRH agonist or were previously treated with orchiectomy and were required to have a serum testosterone level ≤ 50 ng/dL^{1,2}

- ZYTIGA® (abiraterone acetate) [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2011.
- Data on file. Janssen Biotech, Inc.; 2011.

Please click <http://www.urotoday.com/media/jce/mediaplayer/mediaplayer.swf> to listen to the full podcast.

Although medical castration leads to a decrease in the production of testosterone, in mCRPC the prostate cells remain androgen-sensitive and widely dependent on androgens. Adrenal glands and prostate cancer tissue can produce androgens, which eventually leads to continued prostate cancer growth. Blocking androgen production by nongonadal sources is a targeted clinical benefit. One agent, abiraterone acetate (ZYTIGA®), reduces androgen production by blocking the enzyme, cytochrome P450 17 alpha-hydroxylase (CYP17). ZYTIGA® is indicated for use in combination with prednisone for the treatment of mCRPC for those who have received prior chemotherapy containing docetaxel. The mechanism of action is abiraterone, which inhibits the production of androgen in three sites: the testes, the adrenal glands, and the prostate tumor tissue directly.

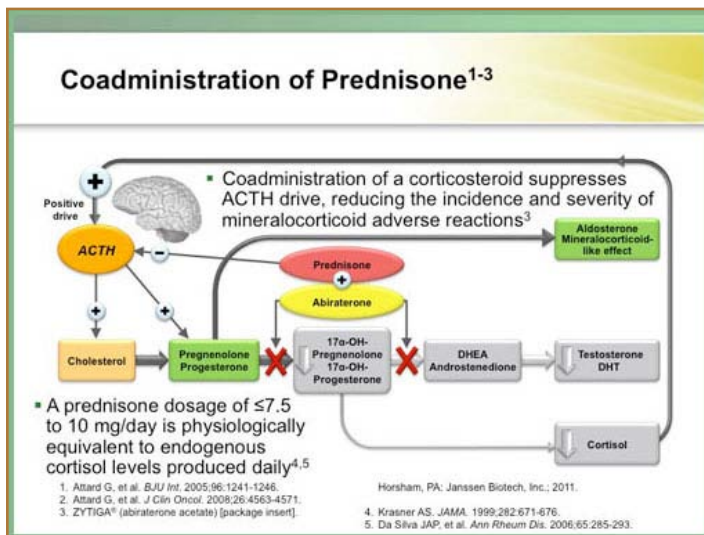
Abiraterone acetate, taken in oral form, is converted *in vitro* to abiraterone [3]. The patients in the abiraterone acetate clinical trial were using GnRH agonist or were previously treated with orchiectomy, and were required to have a serum testosterone level ≥ 50 ng/dL³. This drug works at CYP17: 17 α -hydroxylase and CYP17: C17, 20-lyase level.

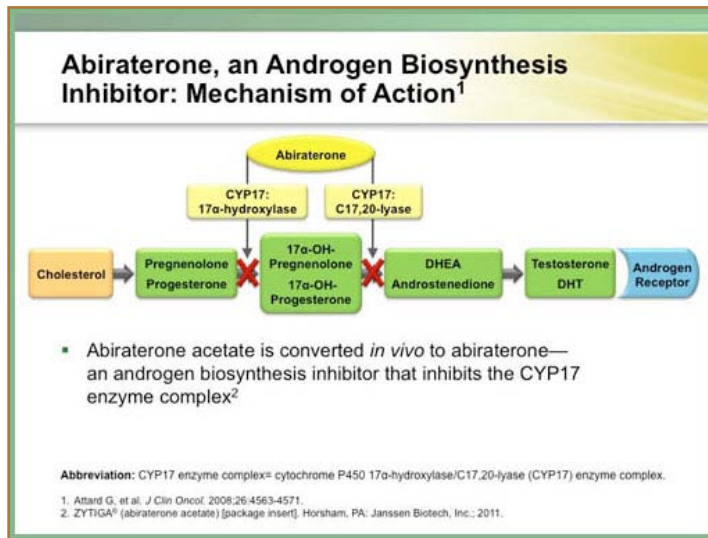
Treatment with ZYTIGA® results in the inhibition of androgen production. The result is decreased serum testosterone and other androgens in patients in the placebo-controlled phase III clinical trial. Low-dose prednisone is prescribed, and it is not necessary to monitor the effects of abiraterone acetate on the serum testosterone levels. With this drug there is a potential mineralocorticoid effect. During the CYP17 inhibition, the cortisol production is blocked, resulting in decreased cortisol levels. The reduced cortisol levels generate a positive ACTH pathway to stimulate cortisol production. Since the cortisol production is blocked, there is the potential to increase mineralocorticoid levels. For this reason, potential mineralocorticoid excess should be monitored as a side effect in the form of hypertension, hypokalemia, and/or fluid retention. In particular, when assessing the patient, make a complete history of cardiovascular disease or other medical conditions that may be compromised by these side effects.

The recommended dosage for ZYTIGA® is 1,000 mg (four 250 mg tablets) taken orally on an empty stomach in combination with prednisone (5 mg, administered twice daily). The administration of prednisone suppresses the ACTH drive, reducing the incidence and severity of mineralocorticoid adverse reactions.

Overview: Results of the Phase III Abiraterone Clinical Trial

The phase III trial began in April 2008 with 1,195 patients randomized with docetaxel-refractory CRPC to either





abiraterone or placebo in a 2:1 fashion. Both arms received prednisone (5 mg) twice daily. The independent data monitoring committee recommended the study be unblinded on August 20, 2010. By this point, abiraterone-treated patients had received a median of eight 28-day cycles, and the patients in the placebo arm had received a median four 28-day cycles. The study demonstrated a median overall survival in the abiraterone-treated arm of 14.8 months compared with 10.9 months in the placebo arm. The abiraterone arm also yielded superior outcomes in time to PSA progression (10.2 months versus 6.6 months, $P < 0.0001$), radiographic progression-free survival (5.6 months versus 3.6 months, $P < 0.0001$), and PSA declines $\geq 50\%$ (confirmed, 29.1% versus 5.5%, $P < 0.0001$). The U.S. Food and Drug Administration approved ZYTIGA® on April 28, 2011. The recommended dose is 1,000 mg daily along with prednisone (5 mg) twice daily. The most common adverse effects seen on abiraterone therapy were joint discomfort, hypertension, and hypokalemia.

Take-Away Messages from Dr. Mouf

“This is important for us as urologists to recognize that the landscape for prostate cancer is changing. That includes our role in all aspects of prostate cancer treatment from early to end-stage disease. Looking at what is approved and



those drugs coming down the pike, ZYTIGA® (abiraterone acetate) is a hormonal agent currently approved by the FDA for the treatment of metastatic castration-resistant prostate cancer after a patient has progressed on docetaxel. ZYTIGA® is also being investigated for its usefulness

prior to chemotherapy and those results look very promising.

ZYTIGA® has many key clinical points when prescribing this drug. In its oral form, ZYTIGA® does have some side effects, but in combination with low-dose prednisone, the mineralocorticoid excess is reduced. A key teaching point is to know how abiraterone acetate works. It works in three separate sites: the testes, the adrenal glands, and the prostate tumor tissue. Most importantly, abiraterone blocks at the CYP17: 17 α -hydroxylase and CYP17: C17, 20-lyase level.

The way the drug works; it can increase the pathway to mineralocorticoid. If you use ZYTIGA® without a steroid, it could cause adverse events such as hypertension, hypokalemia, or fluid retention. For this reason, the drug is taken with low dose prednisone given twice a day, and by doing that, the prednisone helps block adrenocortical insufficiency. When first starting ZYTIGA®, the FDA requires that the patient’s liver function be monitored every two weeks.

A key patient instruction point is taking this oral agent in the right way, in terms of diet and what’s in their stomach. I recommend the patient take ZYTIGA® before breakfast. The ideal time is 2 hours before breakfast, then waiting one hour before starting breakfast, and then taking prednisone with breakfast and with dinner.

In May of 2012, ZYTIGA® was officially approved for the treatment of (mCRPC) in men who have progressed on docetaxel.

In summary, ZYTIGA® (abiraterone acetate) inhibits CYP17, an enzyme complex needed for androgen biosynthesis, and when used in combination with prednisone, improved overall survival in patients with mCRPC who received prior chemotherapy containing docetaxel. The clinical trial demonstrated a survival advantage of 4.6 months—that’s a 41% difference in median

Overall Survival: Updated Analysis

| Intent-to-Treat Analysis | Abiraterone Acetate Plus Prednisone (n = 797) | Placebo Plus Prednisone (n = 398) |
|--|---|-----------------------------------|
| Deaths (%) | 501 (63%) | 274 (69%) |
| Median Overall Survival, Months (95% CI) | 15.8 (14.8, 17.0) | 11.2 (10.4, 13.1) |
| Hazard Ratio (95% CI)* | 0.740 (0.638, 0.859) | |

- 4.6-month difference in median overall survival
- 41% difference in median overall survival

*Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate
ZYTIGA® (abiraterone acetate) [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2011.

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overall survival, which was highly statistically significant. Overall, ZYTIGA® has a good safety profile.”

When asked, when to stop ZYTIGA®, Dr. Moul replied, “As we found in the study, the patient is discontinued on this treatment plan if all three criteria for disease progression are met: 1) a 25% increase in PSA over baseline; 2) protocol-defined radiographic progression; or 3) symptomatic or clinical progression.” Dr. Moul reminded colleagues during the session that ZYTIGA® should not be stopped simply due to a rise in PSA.

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ADDITIONAL READING

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