Prostate cancer (PCa) is the most common cancer among men. Improvements in the screening and the management of the disease have led to earlier diagnosis and longer life expectancy of patients. Therefore, the multiple side effects associated with actual treatment options, the quality of life of these patients has become increasingly important.

Advanced prostate cancer arises in several forms, either recognized because of rising prostate-specific antigen (PSA) after failing primary treatment or, more ominously, bone pain or urinary symptoms signifying locally advanced disease and or metastatic disease. Fortunately, the latter is rare in the modern era. All of these entities, however, are driven by ongoing stimulation and downstream signaling from the androgen receptor (AR). By eliminating ligand (namely serum testosterone), this activity can be markedly downregulated as first discovered by the work of Huggins and Hodges in 1941, who were ultimately awarded the Nobel Prize in 1966. Since that time, bilateral orchiectomy has been replaced with androgen deprivation therapy is the mainstay of treatment for men with metastatic prostate cancer and has been shown to improve survival in combination with radiation therapy in men with high-risk localized disease.
medications, including luteinizing hormone releasing hormone (LHRH) agonists, GNRH antagonists, and combined androgen blockade (CAB). The effect of these regimens, however, is limited, as nearly all patients with advanced disease will, if maintained on androgen deprivation therapy (ADT), develop resistance requiring alternative therapies.

ADT is the mainstay of treatment for men with metastatic PCa and has been shown to improve survival in combination with radiation therapy in men with high-risk localized disease.1-3 It is also commonly used to treat men with biochemical relapse, especially when classified as high risk. Unlike bilateral orchiectomy, medical castration is reversible and may be used on an intermittent basis. ADT is associated with characteristic side effects including hot flashes; decreased libido, decreased bone mineral density, loss of body mass, muscle mass, and strength; increased body fat, weight; insulin resistance; cardiovascular toxicity; and emotional and cognitive changes.4-6 The potential physical benefits of an intermittent regimen with one or more off-treatment periods are considered to be due to complete or partial testosterone recovery allowing moderation of side effects and improvement of quality of life (QoL).8

This issue of Grand Rounds in Urology reviews the current and future use of ADT in treating advanced prostate cancer, but with cost of healthcare an ever growing factor in treatment decisions, it will also examine the potential use of older antiandrogen therapies in treating patients with advanced PCa.

REFERENCES

Hormone Therapy in Prostate Carcinoma

This article was developed from the transcript of a lecture presented at the 25th Perspectives in Urology: Point Counterpoint on November 8, 2016, in Scottsdale, Arizona.

Contributor:

Robert E. Donohue, MD
University of Colorado, Denver
Aurora, Colorado

Dr. Donohue graduated from the New York University School of Medicine and completed his Surgery and Urology residency at NYU. He was appointed Special Fellow in Urology at the Memorial Sloan-Kettering Cancer Center. Spending some time abroad, Dr. Donohue became the Senior Surgical Registrar in Urology at the Christchurch Public Hospital in Christchurch, New Zealand. Back in the USA, he was appointed Assistant Professor of Surgery for Urology at The University of Colorado in 1972 and Director of Medical Student Programs in Urology there, as well as the Chief of Urology Service at the Denver CAMC, in 1977. He was promoted to Associate Professor in 1979 and Full Professor in 1989.

Other positions Dr. Donohue held include being program chairman of the Rocky Mountain Urological Society from 1975-1988 and President from 1994-1996. He served as President of the South Central Section of the AUA in 2004. Dr. Donohue retired in 2009 but he is still attends the Urology weekly Grand Rounds, The Second Opinion Conference of Dr. Crawford for New Urologic Malignancies. Dr. Donohue also still assists in the medical Spanish course for first year medical students.

In order to appreciate hormone therapy fully, there are several historical facts to point out, beginning with Dr. John Hunter, who in 1786 discovered that the prostatic epithelium undergoes atrophy after castration. Dr. J. William White, in 1895, found that castration leads to prostatic atrophy in both dogs and men. In 1935, Dr. Clyde L. Deming said that castration made the primate prostate smaller.

Dr. Waldemar and Dr. Kutscher detected acid phosphatase in the prostates of men and monkeys in 1935. In 1936, the Gutmans detected acid phosphatase in the primary prostatic cancer and the metastatic tumor, and in 1938 that acid phosphatase increased with testosterone therapy. In 1938, Dr. B.S. Barringer and Dr. H.Q. Woodard, as well as the Gutmans again, found elevated acid phosphatase in the primary prostate cancer itself and in metastasis.

In 1944, Dr. Charles Huggins found that benign and malignant epithelium are biochemically analogous and respond in a similar fashion to castration.

In 1941, Huggins performed bilateral orchiectomies in 21 patients; three of those patients did not respond to the bilateral orchiectomy or to the subsequent administration of ethinyl estradiol. Huggins noted that the patients who didn’t respond were those with small testes. He defined this as the hypogonadal state and he’s probably the first to term this castration-resistant prostate cancer. He also investigated the adrenals being a source of androgens in a 1945 study, with a series of four patients with sequential bilateral adrenalectomy without adequate glucocorticoid and mineralocorticoid hormonal replacement therapy. In 1951, Murphy and Schwappart proposed the study of an FSH rise and its possible deleterious effects following orchiectomy.

The androgen receptor is a ligand-inducible transcription factor that drives expression of genes for growth, recurrence, and metastases in prostate cancer, and is is activated by a steroid hormone and antigen. It binds to the C terminal that is the carbohydrate terminal of the ligand binding site on the gene. The transcription factor then transfers the androgen receptor plus androgen from the cytoplasm into the nucleus where it interacts with the DNA and then copies itself. It is then extruded into the cytoplasm as messenger RNA after the introns have been removed from the gene and then does its act. But the androgen receptor can become hypersensitive to lower androgen levels, and can amplify itself. It is promiscuous for other ligands. Mutations increase with androgen receptor activity and their outlaw androgen receptor models, which can respond to other things. So, the androgen increases the androgen receptor transcription without androgens. It increases co-regulators, parallel and alternative survival can go on, and lurker cells can model stem cells that interfere.

Androgen receptor V7 splice variant is a mutation in the splicing the messenger RNA of the androgen receptor that allows the androgen receptor to bind to the gene, but lacks the C terminal where the Enzalutamide and Abiraterone are attached, but not the N terminal where the androgen receptor binds. Enzalutamide and Abiraterone are rendered ineffective.

With V7 (AR-V7) what happens is that the exons and introns are transcribed from the DNA into RNA. The exons produce the protein; the introns are filler and we have no idea, even today, of what their exact role is. But what happens is when the messenger RNA splices out the introns, the two edges of the exon, the first exon and the second exon, adhere together and variations in the androgen receptor occur by fusion, which is now called a splice variant.

The paper by Pound on the natural history of progression after radical prostatectomy had to do with biochemical recurrence. The time from biochemical recurrence to metastases is about eight years, and the time from the metastases appearance to death is five years later. That’s approximately 14 years.
What we want to do is ADT. There are four different ways we can do this: ablate the source, use antiadrenal androgens, we can inhibit LHRH or GNRH release, and we can inhibit androgen synthesis. (Figure 1)

In terms of side effects, there is osteoporosis, which we treat with calcium, vitamin D, and either oral or parenteral bisphosphonates. Also hot flashes, which we have various treatments for to decrease the intensity and occurrence. Gynecomastia and mastodynia are really vicious side effects. We use spot radiation for the gynecomastia to help prevent it. This must be done before starting the first hormonal manipulation or it will not work. Other side effects include loss of libido, impaired cognitive function, body habitus changes, diabetes and metabolic syndrome, cardiovascular side effects, fatigue, and anemia. (Figure 2)

What can we do? We can ablate the source in the androgen axis blockade. We can do a bilateral orchiectomy or subcapsular orchiectomy. The subcapsular orchiectomy must be done completely because there are LHRH receptors in the subcapsular tissue, which have to be removed, so it has to be a very meticulous subcapsular orchiectomy. I, myself, would do the orchiectomy and sew the components of the spermatic cord together and that would be the remnant you would have in the scrotum.

In terms of side effects, there is osteoporosis, which we treat with calcium, vitamin D, and either oral or parenteral bisphosphonates. Also hot flashes, which we have various treatments for to decrease the intensity and occurrence. Gynecomastia and mastodynia are really vicious side effects. We use spot radiation for the gynecomastia to help prevent it. This must be done before starting the first hormonal manipulation or it will not work. Other side effects include loss of libido, impaired cognitive function, body habitus changes, diabetes and metabolic syndrome, cardiovascular side effects, fatigue, and anemia. (Figure 2)
isomer was used. With castration versus Bicalutamide, the quality of life is better with Bicalutamide, but gynecomastia occurs in 86% of the patients and mastodynia in 72% of the Bicalutamide treated patients. These are some of the problems that have been reported with Bicalutamide. Nilutamide has a 56-hour half-life, but 25% of patients experience delayed adaptation to darkness after exposure to bright light, and Enzalutamide is an AR antagonist that blocks nuclear translocation, but rarely can cause seizures as a side effect.

With respect to overall survival with anti-androgen withdrawal, despite the PSA decrease, there is no overall prolonged survival. With flutamide studies you have to leave everybody off for four weeks before you can initiate another nonsteroidal anti-androgen. With Bicalutamide and Nilutamide, you have to wait six weeks.

The third approach is the inhibition of LHRH and/or LHRH release, and we have a variety of agents here. With the removal of one amino acid, leucine, and the amino acid sequence of ten, and you have the LHRH analog. As Dr. Crawford says, you remove seven amino acids and you get the LHRH antagonists. The names of the antagonists you’re all familiar with: Cetrorelix, Abarelix, and now we have Degarelix.

What is a flare? How long does it last and is it clinically significant? Flare is an elevation in a hormone or an enzyme associated with a therapeutic effect, which is the injection of the next dose of the LHRH. The LHRH flare occurs every time the GHRH injection of the next dose of the LHRH. The flare occurs every time the GHRH injection of the next dose of the LHRH, and now we have Degarelix.

Dr. Crawford was an author of the SWOG study, and I recommend everyone read the paper. Marote clearly states in his study that if the serum testosterone goes above 32 nanograms per deciliter, which we now have an exquisite way of measuring, then there is a problem with survival. So, 32 nanograms is the sum to remember. The GNRH antagonist does not have flare.

The PSA bounce after primary therapy with either external beam radiation therapy or brachytherapy is much more difficult to interpret. Between 36 and 60 months after termination of the therapy, the PSA starts going up, and no one knows whether or not it’s a tumor or bounce. We never know whether this is a benign bounce or a tumor recurrence, and the problem is it can last from three to five years.

We have had studies with LHRH analog versus DES, LHRH analog with antiadrenal androgen, and orchiectomy and antiadrenal androgen, but, while the studies themselves are important, the most important thing that came up in these studies was the osteolytic effects, the increased osteoclastic activity from the hormone manipulation, so that we need to also monitor calcium, vitamin D, and bone health.

The summary of all combined androgen blockades in 27 studies in metastatic prostate cancer, is that there is five-year survival, with combined androgen blockade 25% versus 23%, and that is the problem. Five years may not be an appropriate endpoint since the average survival rates are between 28-36 months

Concerning initial therapy for localized prostate cancer for cure with three months of neoadjuvant androgen deprivation therapy, before primary therapy, radical prostatectomy in non-randomized trials, the positive margin rate in the surgical specimen went from 50% to 15%. In three randomized prospective neoadjuvant ADT studies, followed up at 15 months and four-to-seven years, where the patient received three months of ADT and a radical prostatectomy versus a radical prostatectomy alone, there was no PSA progression difference.

Radical prostatectomy is the removal of the entire prostate, the seminal vesicles and at times, lymph nodes of the pelvis. With neoadjuvant and adjuvant ADT with external beam radiation therapy, however, that is not the case. There is better overall survival, cancer-specific survival, and disease-free progression. But the problems with these LHRH agonist or GNRH antagonist —6 months, 12 months, 18 months, 24 months, or 36 months? When you deliver primary radiation therapy with an intact prostate, you give the antiadrenal androgen for the duration of the radiation therapy and in some trials continue as long as patient is receiving hormonal ablation. The LHRH analog continues for 4, 6, 12, 24 or 36 months. At the present time, in any study the radiation oncologists are trying to get a patient to stay on the LHRH analog after 12 months, but because of the side effects, which we’ve already discussed, they are very, very unlikely to be successful in getting the patient in a study with the radiation oncology groups to stay on the LHRH analog for more than 12 months. Remember, antiadrenal antigens for the course of the radiation and then the LHRH analog or GNRH antagonist continues for a variable length of time up to 36 months.

With regard to continuous versus intermittent therapy, there are two studies where intermittent therapy was shown not to be inferior in a study by Crook, and then in the most recent study by Hussain, it was shown not to be superior, so you take your choice.

The last therapy we have is inhibition of androgen synthesis and we have Aminogluthethimide, Ketoconazole, and of course, Abiraterone.

The adjuvant study done by Messing showed that immediate orchiectomy or LHRH analog initiation, which means within 120 days of the operation, in patients with positive nodes, led to 18 deaths; eight from cancer of the prostate. If you did delayed hormone therapy and the delay was variable among the study groups, they recommended initiating it when a PSA reached 10, or a PSA reached 20. There were 28 deaths; 25 of them were from cancer of the prostate. That definitely showed an advantage to early ADT in men with positive nodes found at the time of a radical prostatectomy.
The ECOG study showed no advantage and in the EROTC study, when they found positive nodes, they did not do the radical prostatectomy. So, the primary remained intact, which is a very important consideration. In the ECOG study, with the prostate intact, there was no difference in survival. It seems that if you present with positive nodes at the time of your radical prostatectomy, either diagnosed by frozen section or diagnosed later, the studies clearly show you must go on the LHRH analog possibly for PSA, there’s a 75-month survival. If the PSA nadir stays at four ng/dl or above, there is a 13-month survival.

In combination studies with radiation and orchiectomy versus radiation, every study shows the combination beats radiation therapy alone. These are just the years that these agents were introduced. With the introduction of Methotrexate in 1999 and Docetaxel in 2004, some physicians say that medical oncologists are too self congratulatory for a three or four-month survival. Ask the patient what he or she thinks of a three or four-month survival, and only the medical oncologist will congratulate himself; the patient won’t.

We have orchiectomy, DES 3 mg, the other treatments for hormone-refractory disease, selective adrenalectomy now done medically, selective hypophysectomy now done medically, the antiadrenal androgens, and the LHRH analog, or the GHRH antagonist, in combination with the antiadrenal androgens, and in castrate-resistant prostate cancer. Remember CRPC was diagnosed in 1941, but we didn’t use that terminology. Now we have Docetaxel, and the other new agents from 2004 on, initially given only after CRPC was diagnosed.

As you’ve heard previously, we can now give Abiraterone and Enzalutamide up front, and we can give Docetaxel with initial hormonal therapy with a phenomenal result. As Dr. Petrylak said earlier, you can now use Sipuleucel-T, reuse it, give it a second time, etc. All bets are off at the present time as to what we do and in what order. Instead of options being clarified with the recent Abiraterone, Enzalutamide, Docetaxel and Sipuleucel-C studies, it gets more confusing.

**REFERENCES**


This review will cover some new concepts in ADT. Of course this all goes back 70 years to Dr. Huggins, who established the fact that prostate cancer could be treated with hormones. But it was very interesting that in his Nobel Laureate presentation in 1966 he made a statement, “Despite regressions of great magnitude, it is obvious there are many failures of endocrine therapy that control the disease.” This possibly may be the first verbal description of castrate-resistant prostate cancer way back in 1966. (Figure 3)

Everything we do today is based on the fact that androgen deprivation therapy remains the basis for advanced prostate cancer. I’m going to try to focus on advanced prostate cancer just so it doesn’t get too confusing between using hormones for radiation, or using them for rising PSA. But the bottom line is no matter where you are in this continuum, the fact is that androgen deprivation therapy is continued to maintain as low a testosterone state as possible.

Of course we now know that prostate cancer flips over to a castrate-resistant state as it progresses through a whole variety of potentially genetic alterations, including tumor androgen synthesis and alterations in the androgen receptor, but the bottom line is that in spite of castrate levels of androgens, the tumor is still dependent on low levels of androgens.

We know that there are now many sources of androgen production and I’m leading up to a new concept I want to present concerning androgen deprivation therapy—we know that standard androgen deprivation therapy takes care of testicular as well as other androgen precursors, such as from the adrenal glands. These newer androgen pathway blockers can also block the intratumor androgen synthesis and signaling pathways.

Prostate cancer survives routine androgen ablation by synthesizing androgens and an amplified number or mutated androgen receptor. The androgen receptor

---

**New Concepts in ADT**

This article was developed from the transcript of a lecture presented at the 17th Future Directions in Urology Symposium on September 13, 2016, in Colorado Springs, Colorado.

**Contributing Author:**

Leonard G. Gomella, MD
Thomas Jefferson University
Philadelphia, Pennsylvania

Dr. Gomella is the Bernard W. Godwin, Jr. Professor of Prostate Cancer and Chairman of the Department of Urology at Jefferson Medical College. Originally from New York, he completed medical school, general surgery and urology training at the University of Kentucky in Lexington, Kentucky. After a Urologic Oncology Fellowship in the Surgery Branch of the NCI in Bethesda, Maryland, he joined the faculty of Jefferson Medical College in 1988 and was appointed Chair in 2002. He is also Associate Director for Clinical Affairs for the Kimmel Cancer at Jefferson and Urology Chair for NRG/RTOG, serving as lead Urology investigator on multiple national trials. In 2008 he was named Clinical Director of the Jefferson Kimmel Cancer Center Network.

Dr. Gomella is involved in both translational basic science and clinical research in the development of new diagnostic techniques and treatments for prostate, bladder and kidney cancer through Jefferson’s Kimmel Cancer Center. Dr. Gomella’s team was first to use RT-PCR to detect circulating micrometastasis in patients with prostate cancer, a discovery that led to a new field of investigation in this disease. Dr. Gomella is also recognized as an early contributor to urologic laparoscopy, initiating the program at Jefferson in 1990. He has given over 500 presentations at local, national and international meetings and written over 350 papers, chapters and monographs in the field of Urology.

---

![Figure 3. The ADT continuum in advanced prostate cancer](image-url)
Androgen deprivation therapy remains a core principle with advanced prostate cancer.

Three concepts I want to review. The first is the new androgen receptor pathway agents for CRPC, both the approved and the investigational. Another concept is the possibility that we can prevent or limit castrate-resistant prostate cancer, and lastly, optimizing the choice of agents for ADT.

We know the newer agents we have available and are approved for metastatic CRPC and have been using them routinely for several years. There are several investigational androgen receptor pathway agents that we're working with. The development of TAK700 was unfortunately ended a couple of years ago. TOK001, a multifunctional androgen receptor blocker may or may not be moving ahead based on recent clinical trials. ARN is no longer called ARN, but apalutamide, and is an androgen receptor blocker. A relatively new one with not much data out there, is ODM-201, which is interesting. It's an androgen receptor blocker but it also appears to act on the mutant androgen receptor.

This is the overview of androgen receptor pathway blockers for mCRPC. You'll notice a lot of them have very similar chemical structures, and others have unique structures that make them have different characteristics clinically. Where these various new androgen receptor pathway agents fit in the pathway from androgen-sensitive through androgen- or castrate-resistant prostate cancer is shown in the figure. (Figure 5)

Certainly we got a big wakeup call a couple of years ago with abiraterone through its CYP17 and C21 lyase activity giving us low levels of testosterone circulating androgens that we have never seen before. In fact many of our laboratories are no longer able to measure these very low levels. Enzalutamide is not only an androgen receptor blocker, but it also has translocation and transcription effects in the cell, so it actually goes beyond being an androgen receptor blocker. At present the leading phase 3 clinical trials involve ARN-509 and ODM-201.

Looking at galaterone's CYP17 inhibition it also is an antiandrogen. Although it's structurally similar to abiraterone, it also blocks the androgen receptor. ARN-509 has a lot of similarities to enzalutamide. ODM-201 is an antiandrogen, but it's very interesting. It is structurally unique from some of the other agents and may have activity with mutant androgen receptors.

I'm not going to get into detail because there is a lot of talk about the clinical trials, but just to make some points. Galaterone, in the ARMOR2 study basically was very interesting. It looked like it was agnostic to the AR-V7 receptor mutations, so there's obviously potential excitement for that drug in the AR-V7 mutant space. The ARMOR3 study right now is a specific study looking at AR-V7 comparing that with enzalutamide. Early data suggests the agent is not reaching the expected outcomes.

Apalutamide (ARN-509) is a new generation androgen receptor inhibitor. The dose is 240mg a day. You see very significant PSA responses in the first trials with it in the Phase I studies, Phase II studies, and with M1 disease.
This just one example of a trial out there, the SPARTAN trial, comparing ARN-509 to placebo in men with nonmetastatic castrate-resistant prostate cancer. There are many trials out there, but a couple show what is going on with some of these agents.

ODM-201 is very different than apalutamide and enzalutamide. One of the issues, and this is in animal studies, I’m not aware of any human studies regarding the blood brain barrier, but these issues may become important going forward when we look at side effect profiles on some of these. The ARAMIS study is again one of the ODM-201 studies looking at men with high risk nonmetastatic castrate-resistant prostate cancer, comparing the compound with the placebo. (Figure 6)

In want to discuss options for preventing and limiting castrate-resistant prostate cancer, is there anything new on intermittent hormonal therapy? Intermittent hormone therapy is out there. It’s practiced, we know a lot about intermittent hormonal therapy, because it’s been around for 25 years now. We know it improves the quality of life as it limits side effects. It’s very important if you’re going to do intermittent hormonal therapy to carefully monitor the patients.

One of the theoretical goals and why intermittent hormonal therapy became popular was to prevent or limit the development of castrate-resistant disease. We have not really proven that yet, but the bottom line is that it appears to be noninferior to continuous androgen ablation. And I think we have to learn a lot more about actually how, or what the optimum intermittent hormonal therapy approach is. Everybody has different trigger points for restarting the androgen ablation therapy.

There was a major review last year of intermittent hormonal therapy. Most trials demonstrate slight improvements on physical and sexual function with hormonal therapy, but there is no significant difference between intermittent and continuous hormonal therapy.

The EAU in 2012 accepted intermittent androgen therapy, and since 2015 it’s now very positive on intermittent androgen therapy. ESMO is mixed, it is recommended for men with biochemical relapse after radical radiation and ongoing radiation therapy. NCCN has become more positive, demonstrating that it’s consistent with quality of life. NCCN talks about risk stratification of these patients based on the SWOG. Maha
Hussain is basically saying that if you have a good response, think about continuing intermittent therapy with a low nadir PSA. If you don’t have a good response, should use continuous androgen blockade. Intermittent androgen ablation is something that can be considered in certain well informed patients.

A paper came out very recently on men with androgen naïve prostate cancer, called the BATMAN study. The primary endpoint was met, with 60% of the patients having a PSA of less than 4 at 18 months. No survival data are available, but this is a novel approach to attempt to limit the development of castrate-resistant prostate cancer.

With androgen receptor targeted therapies, we talked about identifying the AR receptors. Identifying subtypes of muted androgen receptors, such as AR-V7, may give some indication on which tertiary hormonal therapy patients may or may not respond. The AR-V7 mutant may impart resistance to enzalutamide and abiraterone.

Data suggests that the mutated AR-V7 androgen receptor may be very dynamic based on the milieu that the prostate cancer is exposed to, so patients who stay AR-V7 negative have a fairly good PSA response. Those who go from AR-V7 to AR-V7 negative to AR-V7 positive have a lesser response, and those who persistently present with the mutant AR-V7 gene really don’t have a good response at all.

The availability of these predictive biomarkers may help us going forward. A new discover is the inherited HSD3B1 gene that may be predictive for who should get androgen deprivation therapy, or those who may require therapy such as chemotherapy. If you’re a wild-type HSD3B1, you do reasonably well. If you’re heterozygous, not so well, and if you have the homozygous variant, you have a really rapid downhill course when it comes to PSA progression. We all have patients like this, they do great on hormonal therapy, and other patients go downhill very rapidly.

REFERENCES


A Roundtable Discussion on the Use of Older Antiandrogen Therapies

Roundtable Participants:

**Gerald L. Andriole, Jr., MD**  
Washington University  
St. Louis, Missouri

**E. David Crawford, MD**  
University of Colorado, Denver  
Aurora, Colorado

**Raoul S. Concepcion, MD**  
The Comprehensive Prostate Center  
Nashville, Tennessee

**Leonard G. Gomella, MD**  
Thomas Jefferson University  
Philadelphia, Pennsylvania

**Daniel P. Petrylak, MD**  
Yale Cancer Center  
New Haven, Connecticut

**J. Clifton Vestal, MD**  
Urology Associates of North Texas  
Arlington, Texas

**DR. CRAWFORD:** I’ve taken a beating about antiandrogens, a big beating over the years. It’s very interesting now that people are all interested in lower T and how low can you get with the abiraterone or block with enzalutamide, and that and kind of ignores what we were trying to show years ago with combined androgen blockade. It’s interesting, people used CAB to block flare. We’ve done a lot of audience response questions over the year on who uses it long term, and most urologists claim to use long term. And most of the studies that were done in the Southwest Oncology Group and RTOG, used combined androgen blockage from the beginning to end.

There are a lot of arguments over the role of antiandrogens, going back to Ferdinand Labrie and Nick Bruchovsky years ago, and then the Europeans and the studies that were done by Frans Debruyne and his colleagues.

Flutamide is a first generation, nilutamide and bicalutamide are second. Nilutamide wasn’t really well studied in the U.S. But it will be interesting to see where we go. I’m not surprised that there’s some current interest in it.

**DR. PETRYLAK:** I’m head of the GU section at Yale. I have been there for the last four years, and we’ve been developing translational work in prostate and bladder cancer. I’ve actually got two patients on nilutamide right now, both of whom have asymptomatic PSA rises and non-metastatic disease. That’s where I’ve used the drug the most, in this situation. So I think the drug does have activity, there’s no question. It is active after drugs like bicalutamide, so we really want to help make the prostate great again.

**DR. CONCEPCION:** Dan, is that true of all antiandrogens? On the sequence, the next one always does a little something?

**DR. PETRYLAK:** Perhaps. But my sense is that there’s maybe a little more activity with this as a single agent.

**DR. ANDRIOLE:** I’m from Washington University in St. Louis, and my recollection is that one of the non-inferiority studies for this one was in Europe—it was orchiectomy plus placebo versus orchiectomy plus nilutamide. And the criticism as I remember it was, it was subcapsular orchiectomy and the fear or the thought was, they’re leaving a few Leydig cells behind, and sure, it was a no brainer. I know the bicalutamide study by Klotz and Schellhammer was against LHRH analogs and it just seemed to be more geared towards the U.S. use of hormone therapy.

**DR. CRAWFORD:** There’s a lot of controversy about that, but now the problem with all the European EORTC studies is that they included locally advanced as well as metastatic, so hard to compare to US studies.

**DR. CONCEPCION:** I think that we should specifically have this discussion outside of the area of metastatic castration-resistant prostate cancer, because again, I don’t think there’s any role of using first generation antiandrogens. Given the fact that we have basically now enzalutamide and now the second generation androgen biosynthesis inhibitors like abiraterone I think we’d like to limit the discussion to potentially other uses in the biochemical recurrence phase as monotherapy.

**DR. CRAWFORD:** So we’re sort of going back to the beginning here with the antiandrogens. If I remember correctly, the binding affinity for the receptor is much better than flutamide, and comparable to bicalutamide. I mean quite honestly, the issues with nilutamide and the loading dose have sort of been overcome with a lot of drugs now. The second thing was, truck drivers didn’t do very well with this agent driving at night since light to dark adaptation issues. The third, which might be good in some people is the antabuse-like effect that occurs with the drug, and that was basi-
cally it. But it was sort of thought to be a better drug, I mean certainly a better drug than flutamide, and maybe comparable with bicalutamide.

DR. PETRYLAK: Do you have the diagram of the binding sites? If I remember correctly the site on the androgen receptor, the binding site, is different than bicalutamide.

DR. CRAWFORD: If you can start separating that from the first, second-generation thing. If you talk about binding and different responses, we know this. We’ve seen this because we did have a trial, and I think you should go back and look at this trial that Oliver Sartor did in SWOG. It was a large Phase II trial with hundreds of people where we looked at response to antiandrogen withdrawal and reinitiation of antiandrogen and stuff like that. And I think there were a number of people that had nilutamide in that study. Certainly not as many as flutamide and bicalutamide, where it actually looked pretty good and that was probably 15 years ago.

DR. CONCEPCION: I’m assuming that there’s data that basically backs up the bicalutamide data that, given long term it becomes a partial agonist like flutamide correct? Do we know that data?

DR. CRAWFORD: Not all the time, but yes.

DR. PETRYLAK: I mean it does become a partial. It is a partial agonist.

DR. CRAWFORD: That was the thing that differentiated enzalutamide supposedly that it didn’t do that. It had a higher binding affinity, does not have a mitogenic stimulation, so does not mutant, and disrupts nuclear translocation.

DR. PETRYLAK: There are case rare reports of enzalutamide withdrawal response.

DR. GOMELLA: In 1997, we wrote the first report of nilutamide antiandrogen withdrawal syndrome, so the concept that with withdrawal you get a standard flutamide withdrawal syndrome goes back 20 years.

DR. ANDRIOLE: We’re all going to have that right, it’s the androgen receptor, it’s not the drug.

DR. GOMELLA: No, it’s not the drug, right, but the point is, they all become partial agonists. That’s my point. With long term or possibly short term, they’ll become agonists.

DR. VESTAL: Even enzalutamide will become resistant?

DR. PETRYLAK: It’s rare.

DR. ANDRIOLE: Why is that? If you look at the structural design of the molecules, what does the enzalutamide look like? Does anybody know? (Figure 7)

DR. PETRYLAK: It’s similar to bicalutamide. But the trouble is nobody really understands, there’s never been clear answers to what the antiandrogen withdrawal is caused by. Now whether it is a muted androgen receptor, whether it is some sort of cofactor, whether it may be different with each different particular molecule, it’s never been clearly defined mechanistically.

DR. CONCEPCION: Cliff, when you look at the comparative toxicities of all three antiandrogens, does that ever play a role in your decision making or with your partners? (Figure 8)

DR. VESTAL: The night vision thing having remembered just now that the first manuscript I co-wrote with Dr. Crawford was on nilutamide. The upside of the whole paper was that it was equal to and better than flutamide and bicalutamide, which wasn’t available when that paper was written. It’s just that it was better than flutamide and had a better dosing schedule. It’s big issue was abnormal vision. And it’s for those of us who do our work with the castrate-resistant as well. For the last two or three years, in every meeting I ever go to for castrate-resistant, the plea is, please don’t give bicalutamide because it keeps us from enrolling those patients in other trials.

I have always believed that complete androgen blockade is better than no androgen blockage to the point where I even put them on dutasteride or something else that will triple block them. However, I’ve been doing that a lot less lately because I do not want to keep these patients from being able to be enrolled in some other trial because that’s exclusionary. Is that not right?

DR. CONCEPCION: Well, you’ve got to have a washout.

DR. CRAWFORD: I think people are gravitating against that though, aren’t they now?

DR. PETRYLAK: Most of the trials, or at least the current trial we have in SWOG, allow you to place the patient on bicalutamide, but if they get randomized to the other arm, they stop it within three months of starting hormone therapy. So that’s really not been a big problem. I think the trouble is that everybody views all these antiandrogens the same at the onset, and bicalutamide is one because it’s easier to give. It’s enough to give flutamide six pills a day, but it’s one pill a day with bicalutamide, once a day, so I think that’s probably the major reason why it runs out. Unfortunately, the ocular disturbances are a
DR. VESTAL: At the time we had not associated anything with macular degeneration, which is what this has to prove—that it does not in any form or fashion associate itself with macular degeneration. To his point, for those of us who want to save enzalutamide for later, I have in the back of my mind the thought that am I predisposing these cancer cells to mutate to be predisposed to enzalutamide failure.

DR. GOMELLA: I remember an African American gentleman who we gave the pill and 24 hours later, he was in the ER short of breath, so it’s almost like he had an allergic interstitial pneumonitis or something like that.

DR. VESTAL: I think there are two classes of pneumonitis you can get, one chronic and one acute.

DR. GOMELLA: Sounds like this guy got the acute.

DR. CONCEPCION: It seems to me that a lot of the community urologists, what they see a lot and what they worry about is the breast tenderness and the gynecomastia.

DR. CRAWFORD: But if you’re on an LHRH agonist, it doesn’t matter what antiandrogen you use, there’s going to be no difference. The issue is that when antiandrogens are unopposed, and everybody knows this, it raises estrogens. Estrogens are aromatized and that’s why it happens.

All this study right here, I agree with you, a lot of class effects. Diarrhea, that was the big problem with flutamide, and they studied that and it may be what they actually the filler in the capsules, not the pure drug. The binder, take lactase, it didn’t happen. The next one is liver toxicity, and those were more significant at least with flutamide and nilutamide than they were with bicalutamide. However, all these things are interesting, but they’ve never been studied against each other, so you don’t know. The night issues, are issues and it’s of concern, but this happened a little bit, some of the blue vision and stuff like that with sildenafil, and that didn’t keep patients from using it. Dan, why are you using it?

DR. PETRYLAK: I use it for the asymptomatic PSA rises.

DR. ANDRIOLE: Cheap formulary additions, I hate to say, are what gets on the formularies today. Forget your binding as adds, all of that sounds good for us around the table and going to ASCO or whatever—at the end of the day, the market is going to be driven by cost.

DR. VESTAL: What is bicalutamide?

DR. CRAWFORD: Bicalutamide generic is about $350.

DR. VESTAL: So what is nilutamide generic?

DR. CRAWFORD: Right now there’s not a nilutamide generic. It’s coming out soon.

DR. CONCEPCION: If one asks if there is a way to raise the overall level of awareness with the community urologist or medical oncologist who’s prescribing in the MCRPC space, I don’t think there is. I’ve got a lot of patients that just when they get a biochemical recurrence, and you go through and you watch their doubling time, you know where they’re heading, they just do not want to go on LHRH. So I’ve got a lot of patients like Dan’s who are not on LHRH, but they are on an antiandrogen.

DR. VESTAL: But do you feel as though you’re giving them a good service, despite putting them on an antiandrogen? I know you’ve had patients that have gone years and years just on antiandrogens.

DR. CONCEPCION: Yes.

DR. GOMELLA: My thought was always if the doubling time is low, it doesn’t matter. If the doubling time is higher, it matters. They need radiation if it’s prostate. So I don’t know where that sweet spot is of people who need androgen.

DR. CONCEPCION: Most of my antiandrogen monotherapy, most of my patients have been definitively treated either with surgery, radiation, or a combination of both. Now they’ve got a biochemical recurrence, most of them have higher grade Gleason’s at the time.

DR. VESTAL: So his thought about doubling time would probably come to bear as to whether you put them on an antiandrogen or not. If it’s a very long doubling time, you can make an argument, why do anything, right?

DR. CONCEPCION: Well I have patients with radiographic nodal disease that said, “I don’t want the shot,” and we’ll put them on an antiandrogen, and lo and behold, they’ll respond. We all have anecdotal cases like that.

DR. CRAWFORD: There are a lot of studies done that were done early on with bicalutamide monotherapy, and it actually went up to 450mg per day in some of the studies, and it was always close to goselrin. So they tried to get approval with the huge trial they did, the international monotherapy trial, and that got dinged on...
cardiovascular and a few other things. But it’s close, and like you said, there are a lot of people that don’t want it. I have people out 15 years on antiandrogen monotherapy for biochemical failure, things like that. Judd Moul and I wrote that up a number of years ago. I’m interested in why Dan is using it because there may be a market there. What’s going on?

**DR. PETRYLAK:** Both of these patients have asymptomatic rising PSAs, they have nonmetastatic disease. They’re castration-resistant, and they’ve had hormones.

**DR. CRAWFORD:** There’s nothing approved in that arena right now anyway with this stuff. So you’re using it?

**DR. PETRYLAK:** Yes, I use it and there’s activity with it, and I treat about two to three patients a year just like that. They don’t want to go on chemotherapy because they don’t want the steroids.

**DR. CRAWFORD:** So I would disagree with Raoul to some degree. I think you want to fill a whole bunch of buckets if you can with this because your alternative is enzalutamide or abiraterone, which neither one are approved in that arena right now.

**DR. VESTAL:** I use bicalutamide quite frequently for three or four weeks, and that’s it. Do I have to do the double dosing on nilutamide to get the coverage that I’m looking for? What if what I’m looking for is the testosterone spike? Will I block that with one pill per day of nilutamide?

If I’m giving any drug that spikes the testosterone, and they have bony disease, that’s what it is, flares. I typically give degarelix for the patients with bony disease, but if I’m just giving it in general, I usually just give bicalutamide.

**DR. GOMELLA:** Again, the reason for the double dose initially, even in the orchietomy patient was what, biodistribution of a drug?

**DR. CONCEPCION:** There seems to be an effect once you get a PSA taking your first first generation antiandrogen, then you stop it and then you give them another one, and there seems to be some data on improvement in bone pain in several studies. Dave, what do you think about that?

**DR. CRAWFORD:** There are no comparative studies, and that’s the issue. But you know what, there’s nobody out there talking about antiandrogens, and you have to sort of resurrect to see the data. Basically, what Cliff’s study showed is a significant survival benefit with bilateral orchietomy. The results of the initial trials with antiandrogens were LHRH agonists were bad drugs and flutamide made them look good. Well, guess what guys, that study was done to show that an antiandrogen with bilateral orchietomy worked. Now the SWOG study did and didn’t work—it depends on if you look at the glass that’s half full or half empty; it was not designed for the same as the initial trial, and it could be FSHs or other things that go into it. You’ve got an audience of urologists who haven’t heard anything about an antiandrogen or CAB for a long time.

**DR. CONCEPCION:** So what about the concept to use in patients who had failed their first antiandrogen? This study was published in 2001. Nilutamide is a second line hormonal agent with basically a small number of patients. And then you have another article here, again after androgen ablation fails. And again another small study, 28 patients, and in both you’re going to get a little bit of a response. I think this concept of it, I mean that becomes a difficult patient for all of us in the community.

**DR. VESTAL:** Raoul, if you give the drug and it doesn’t work, what do you do them?

**DR. CONCEPCION:** You mean if you give it as second line?

**DR. VESTAL:** Well, I think I would probably not do a doubling time, a poor doubling time ever with an antiandrogen. I think I would probably wait for something to occur so I can start therapy. But for the lengthy 9 months, 12 month doubling time, I think there would be a reasonable portion of patients that might actually have PSA. It might actually encourage them to take the drug. But I would never do it to a three-month doubling time.

**DR. GOMELLA:** Well, unless you failed both surgery and radiation. I wasn’t thinking about that. Then what are you going to do at that point?
bicalutamide, I don’t have any PK data combined this with chemo. I don’t know if there’s an effect on docetaxel metabolism. The study by Sweeney was done with bicalutamide, and we really don’t know if there’s any effect or not.

**DR. VESTAL:** So Dan, in those types of patients where you’re giving chemotherapy upfront after their primary has been dealt with, are you putting them on antiandrogens?

It’s difficult in a castrate-resistance state, because there’s no data, and you have no survival data.

**DR. PETRYLAK:** Yes. The Sweeney study says bicalutamide, so I don’t deviate from that. The trouble is that there is more toxicity in this group of patients, but it may be dependent upon when you give the chemo. There are some issues about androgen metabolism, and that may affect docetaxel metabolism as well.

**DR. CONCEPCION:** Any other limited studies that you think would be valuable?

**DR. CRAWFORD:** There are a lot of trials done in Europe with nilutamide. Louis Denis did a several. There’s a lot of numbers beyond what’s here, people that have been treated with the drug in comparative trials, and they were in a lot of those EORTC large trials where nilutamide was used instead of bicalutamide or flutamide. I think there was one from Canada. The issue was they patented it as a combined androgen blockade, and I think he did it with nilutamide and it covered all the antiandrogens.

It started in Canada with Nick Bruhovsky and Fernand Labrie. Labrie showed that when you put the combination of two together, like leuprolide or an agonist, and nilutamide, you had superior survival over any other way of using androgen deprivation. People were flying to Canada, flocking left and right to get combined androgen blockade. Then he started using flutamide, and again people were going to Canada. So SWOG did a big trial in the U.S. without really any financial support, and the data from the trial was used to gain an approval. Then people flocking to Canada to get flutamide gradually ceased. Then there was a comparative trial of flutamide versus bicalutamide in the U.S. that was powered for non-inferiority, and there were a lot of issues with the trial not showing it was superior.

The other thing that happened with flutamide is there’s a hemolytic anemia that occurs and people don’t understand why that happened, but that’s an adverse side effect that happens every once in a while. And I’m not sure if it’s a class effect or not, I don’t know I ever saw it with bicalutamide.

**DR. PETRYLAK:** I’ve not seen it with bicalutamide.

**DR. VESTAL:** Have you seen it in the STAMPEDE or those kinds of patients? An increased propensity for hemolytic anemia?

**DR. PETRYLAK:** No, not seen it.

**DR. CONCEPCION:** You’ve got no survival data in the patients who are documented with metastatic. They have radiographic metastatic disease or they would be bone soft tissue visceral disease that shows the survival benefit using first generation antiandrogens, whereas enzalutamide clearly has that survival benefit, right?

The patient that is not radiographically positive yet. We also know that none of the drugs, enzalutamide, abiraterone, none of them, can be used and be paid for in that space.

**REFERENCES**


NEW This Year! 1st International Bladder Cancer Update

IPCУ 27th INTERNATIONAL PROSTATE CANCER UPDATE

Westin Riverfront  Beaver Creek, Colorado

January 24-27  2017

REGISTRATION INFORMATION   www.grandroundsinurology.com/ipcu