Hormone Sensitive Disease/Hormone Refractory Disease

Daniel Shevrin, MD

Senior Attending, Division Hematology/Oncology
NorthShore University HealthSystem
Associate Professor Clinical Medicine
Pritzker School of Medicine
University of Chicago

I. Advanced/Recurrent Prostate Cancer—General Concepts

The natural history of prostate cancer is variable and can be very long. PSA kinetics can be extremely helpful. Androgen ablation therapy, which we call AAT, remains the mainstay of therapy when it comes to advanced, recurrent disease but not for early, localized disease. The androgen receptor remains relevant throughout tumor progression, and more recently, we have found that immune therapy, Provenge, has a role as well. Taxotere chemotherapy also plays a major role in symptomatic disease, and new therapies are becoming available after Taxotere progression.

Of the roughly 10,000,000 men who are at risk for prostate cancer, 240,000 per year are diagnosed and typically treated with local therapy. Some are going to be monitored with active surveillance programs, but local therapy is typically recommended, including radiation, prostatectomy, seeds, etc. Of that group, approximately 30% will fail local therapy and will have a PSA recurrence. Most of those will undergo some form of hormonal management. The natural history can vary greatly from 5, to 10, to even more years, but men will fail hormonal management and go on and require other therapies, including Abiraterone, chemotherapy, MDV-3100 and others. Ultimately, 34,000 men per year succumb to prostate cancer. Additionally, some men are diagnosed with locally advanced disease and don't go through the normal progression, and some men, even fewer, are diagnosed right from the beginning with metastatic disease and have a fast track to difficulty requiring additional therapies.

II. Hormonal Therapy

Dr. Huggins from the University of Chicago is considered the father of hormonal therapy and won the Nobel Prize in describing the effect of castration and how effective it is for the treatment of advanced prostate cancer.

III. Endocrine Axis in Prostate Cancer

Under normal circumstances, the hypothalamus produces LHRH, which then activates the release of LH from the pituitary. LH then circulates in the blood to the testicles, which stimulates them to produce testosterone. Testosterone then attaches to the androgen receptor. The androgen receptor becomes activated and moves in to the nucleus

where it activates the cell to do all sorts of bad things that malignant cells do, spread, invade and cause trouble. Testosterone is also converted to dihydrotestosterone, which also binds to the receptor. The other aspect of testosterone production is with the adrenal glands. ACTH is produced and then activates the adrenal cortex to also produce small amounts of testosterone, which also combine. The LHRH agonists, Lupron and Zoladex, work by basically over stimulating the pituitary so that the LH is exhausted, and after a brief period of going up the LH levels will fall and the testosterone levels will fall. Antiandrogens bind to the receptor and don't allow normal testosterone to attach to the receptor. There are also medications that will block the production of testosterone from the adrenal glands.

IV. First-Line Treatment

First-line treatment can be surgical orchiectomy though most men choose not to do that since there are other options. It does result in an immediate drop in testosterone levels. Most physicians and men choose treatment with LHRH agonists. More recently there is now an LHRH antagonist called Degaralix, which results in an immediate drop in testosterone without the rise in LH. It can be used especially if a flare is something you really do not want to have.

V. Second-Line Treatment

The anti-androgens that are currently available for second-line treatment include Casodex, Flutamide and Nilutamide. These are oral agents, which bind to the receptor within the cell, sit there, and don't allow testosterone or dihydrotestosterone to bind. Anti-androgen withdrawal means that after a patient has been on one of the anti-androgens for three to six months, maybe longer, and the PSA is beginning to rise, the disease is progressing, withdrawing that anti-androgen may result in a favorable response because the receptor is actually mutated or changed somewhat and is now actually stimulated. Ketoconazole is an anti-fungal agent that when used in high doses as an oral agent causes a medical adrenalectomy meaning it will inhibit the production of androgen and other hormones from the adrenal glands. Zytiga and TAK-700 are also now available, which are 17/20-lyase inhibitors.

VI. Ketoconazole

Ketoconazole has been around for many years. It inhibits the cytochrome P-450 enzymes and blocks the synthesis of androgen from the testicles as well as the adrenal glands, which is really what it is mainly used for. The PSA response rate is typically pretty good, around 40%, but the agent does require some knowledge in how to use it. There are some side effects, and there can be serious drug interactions making its use somewhat challenging. Nonetheless, those that use Ketoconazole frequently are able to use it safely and effectively.

VII. Hormone-Sensitive Prostate Cancer

The androgen receptor is the most important target in prostate cancer. An initial lowering of the testosterone targets AR and is effective more than 90% of the time. Cells that are "sensitive" will die, and the PSA almost always declines, often to undetectable levels.

There is almost always a clinical response with for instance tumor shrinkage and pain improvement. There are side effects from the lowering of testosterone, and the treatment is not curative. Some cells do not die and eventually will grow in spite of low testosterone levels.

VIII. Side Effects of Androgen Ablation Therapy

The most common side effect of AAT that men feel or experience is hot flashes. There is also typically loss of libido with associated ED, and there is often weight gain. Muscle weakness typically occurs, which can be minimized with appropriate exercise, and we all recognize now that over time there is a loss of bone density, which can lead to osteoporosis and on some occasions even fracture. More recently we are learning that there are potentially other side effects that can be serious to the cardiovascular system, especially in men who have significant underlying cardiac disease already. There is also growing evidence that it can sometimes lead to elevations in blood glucose. Cognitive effects are somewhat controversial, and men say that they have a little more difficulty with word finding or memory effects when on hormonal therapy. We're not convinced that all men experience cognitive effects, but it certainly can occur.

IX. Intermittent vs. Continuous

What about intermittent versus continuous hormonal therapy? The standard of care for decades has been that once a man starts on AAT it should be continued on an ongoing basis. Over the last 10 to 15 years, however, a fair amount of study has been done on intermittent therapy in which there is a fixed treatment phase of six to eight months. Then there is a variable off phase assuming the PSA drops to very low levels in which the treatment is stopped. The testosterone levels begin to rise as the effect wears off. One must closely monitor both the testosterone and PSA levels as well as the clinical status. There is data that intermittent therapy results in less bone density loss, and there is a suggestion of improved sexual function and quality of life for men when they are not on hormonal treatment. Intermittent hormonal therapy is probably better tolerated, and most importantly several large clinical trials have shown that it is not associated with any worse outcome, which has been shown in both patients that have PSA recurrences as well as those with more advanced disease. Intermittent therapy is an option for some patients requiring androgen deprivation therapy though it may not be appropriate for men with high-grade disease or for men who want to see their PSA levels remain low.

X. Hormone-Resistant Prostate Cancer

In hormone-resistant prostate cancer, the androgen receptor remains critical even in the hormone-resistant state as some cells can grow even with exceedingly low levels of testosterone. The treatment goal is to further target the androgen receptor by depriving it of as much testosterone as possible. In androgen-resistant prostate cancer there may be some amplification of the androgen receptor. In other words, the cell is trying to overcome the condition of very low levels of testosterone by increasing the production of androgen receptor to overwhelm the medication and be able to bind more testosterone. There can be a mutated androgen receptor or changes in various co-activators, which

allow better and more effective binding of testosterone even tiny amounts to the androgen receptor.

XI. Clinical States of Prostate Cancer

Clinically localized prostate cancer under some circumstances can move directly to death if not treated appropriately, but for most patients after clinically localized disease if the patient is not cured the PSA begins to rise. They've never had hormone therapy so we call them non-castrate or castrate sensitive. These patients who are put on LHRH, for instance, can then go on to have to have a rising PSA but still not have metastasis eventually evolving into a situation where there are clinical metastases and ultimately death. Some men have metastases but have never been treated with hormone therapy, and they can also evolve into metastatic disease and ultimately death from disease.

1. Castrate-Sensitive, Non-Metastatic

The castrate-sensitive, non-metastatic group includes men with a rising PSA after primary therapy, and the PSA doubling time is a predictor of risk for metastasis. Those with a PSA doubling time of less than 12 months are more likely to lead to clinically significant disease than those whose doubling times are longer or slower. Androgen ablation therapy is the standard of care, and there is currently one large, randomized study supporting intermittent hormonal therapy in this group of patients. Various new agents are also being studied.

2. Castrate-Sensitive, Metastatic

There is also a group of men with castrate-sensitive, metastatic disease. This is a smaller group of men who present with advanced disease who have never been treated. Metastases are typically in bone, pelvis, and abdominal lymph nodes. There is a wide variation in the natural history, and patients who have relatively good-risk disease meaning that the Gleason grades are not 8 or higher whose PSA kinetics are relatively slow will typically respond to hormone therapy. The time to progression can be three to even five plus years meaning their disease is under control by LHRH agonists for quite some time. Those with poor-risk disease have a shorter time to progression in the range of one to three years. The standard of care is hormonal therapy, androgen ablation therapy, and there is some data supporting the use of intermittent therapy in these patients.

3. Castrate-Resistant, Non-Metastatic

Men who have been treated with LHRH agonists because their PSAs have gone up with hormonal therapy, their PSAs go down to zero and become undetectable but then the PSAs begin to rise again are in a group we call castrate-resistant, non-metastatic. Scans are performed, but there are no metastases. Men feel fine other than the side effects of the hormone therapy, but clearly we know that the cancer is showing signs of progression and showing signs that they are able to progress and grow even with low levels of testosterone. This is defined as a rising PSA on LHRH agonist therapy, castrate testosterone levels, negative scans and no symptoms. This group of patients also has a

quite variable natural history, and PSA kinetics are also helpful. Treatment is typically second-line androgen ablation therapy such as the antiandrogens or a drug like Zytiga.

4. Castrate-Resistant, Metastatic (Pre-Taxotere)

Patients who are castrate-resistant with the presence of metastases are now lumped into the group that is pre-Taxotere, meaning they haven't had chemotherapy. Some of these men have a good prognosis meaning even though we get scans and we see disease, with typically one or more lesions on bone scan, they remain completely asymptomatic. Certainly one can recommend standard Taxotere chemotherapy to men in this group, but we typically do not because we don't feel that the potential side effects of chemotherapy justify the results in men where there are other options. Again, antiandrogens are an option for treatment as well as ketoconazole, Zytiga, immunotherapy and other various investigational therapies. In the group with a poor prognosis, meaning men who are symptomatic, we typically consider the use of Taxotere chemotherapy. There are also investigational chemotherapy combinations, which are currently under development.

5. Castrate-Resistant, Metastatic (Post-Taxotere)

The final group is the men who are castrate-resistant, metastatic (post-Taxotere), men who have received Taxotere chemotherapy but then have gone on to progress after that or during that. This is an area that is rich in new agents. Before these were men who we felt had a very poor prognosis. There were limited options, but that has now completely changed.

XII. Bone Metastases

Men with disease to skeleton are at risk for having skeletal-related events, meaning the tumor in the bone can result in brittle bone resulting in fractures. This can result in spinal cord compression. Fractures may result in the need for surgery, and of course they can cause pain, which requires radiation. There has been a lot of effort to try to prevent, minimize, or lessen the skeletal-related events.

XIII. Skeletal-Related Events

Zometa is a potent bisphosphonate given intravenously every three to four weeks. It inhibits the osteoclasts, which are the cells that resorb bone. It results in about a third reduction in the skeletal related events as well as a postponement in the time that the events can occur. There are side effects, which are generally fairly manageable. Osteonecrosis of the jaw is a rare but uncomfortable and problematic side effect, and flu-like symptoms can occur for one to two days after therapy.

Xgeva is a newer agent, which inhibits a protein called rank ligand. It basically works in the same way by inhibiting the osteoclast. It is given subcutaneously every three to four weeks, and the data seems to show a slightly better reduction in skeletal-related events and time to the first event than Zometa. The side effects also include ONJ and hypocalcemia.

Both of these treatments are FDA-approved for castrate-resistant patients with bone metastases. The American Society of Clinical Oncology takes the position that either of these is acceptable and there is no clear superiority of either drug.