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Hormonal Therapy II: Second Line Hormonal Therapy

Puzzle Points

- In patients who've failed initial hormonal therapy, a standard approach is to initiate ketoconazole.
- Transdermal estradiol is a safe and effective way to administer estradiol to men with prostate cancer and can cause very significant anticancer activity.
- IGF1 plays a very important role in prostate cancer biology.
- In a series of papers, the University of Athens showed that Sandostatinlike drugs, when combined with a steroid called dexamethasone, appear to restore hormone sensitivity to hormone resistant men.
- Eric Small reported that Leukine could slow or even arrest prostate cancer progression.
- Since ketoconazole, estrogen, Leukine, and Sandostatin each attack the prostate cancer cell in a different way, it is possible that these agents might be used in combination with each other or with other agents used to treat prostate cancer.

Second Line Hormonal Therapy

This issue continues our discussion of hormonal therapy. In order to understand this issue, you're going to need to read the first part of the series, Hormonal Therapy, I (Vol 9 #5), so if you haven't taken a look yet, please do so. (Order online at www.prostateforum.com/backissues.htm or call 800-305-2432).

There's actually a class of drugs called second line hormonal therapy agents, which we traditionally use when the treatments we discussed in the last issue fail. Over the past five years, there's been a steady evolution in the use of these agents that make them much more effective. (I find it interesting how small changes in treatment can often mean significant benefit for patients.)

Ketoconazole

Ketoconazole effectively suppresses adrenal androgen production, but also directly kills hormone refractory prostate cancer. In patients who've failed initial hormonal therapy, a standard approach is to initiate ketoconazole. This drug not only blocks adrenal androgens effectively but is also active against hormone refractory prostate cancer. In a well-done clinical trial, Eric Small showed that ketoconazole has a 50% response rate in hormone refractory prostate cancer, making it the most active single agent in that setting. Ketoconazole was traditionally used in doses of 400 mg every eight hours. But this dose is associated with significant nausea, vomiting, malaise, and liver damage. Dr. Small shows that by reducing the dose to 200 mg every 8 hours, side effects are markedly reduced without compromising the drug's effectiveness as a prostate cancer treatment.

Ketoconazole impairs the synthesis of steroids like cortisone. At the dose of 200 mg every 8 hours, ketoconazole doesn't cause any problems if a man's stress level—emotional or physical—is low. But given the trauma of a major illness and the emotional, physical, and financial stress a cancer diagnosis can bring, many men may develop adrenal insufficiency. For this reason, I typically give patients replacement hydrocortisone at doses of 20 mg each morning and 10 mg each evening.

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This poses a severe toxic risk for patients.***

Ketoconazole has a short half-life and needs to be administered every 8 hours by the clock. Additionally, it is only absorbed effectively from the stomach when under acid conditions. For this reason, we recommend that the drug be taken with an acid beverage, such as Coke, Pepsi, or a fruit juice. The only exception to this is grapefruit juice, which disables the liver's ability to clear ketoconazole from the body. This poses a severe toxic risk for patients.

The final issue which makes ketoconazole using complex is that the drug interferes with the body's ability to clear half of all prescription drugs, including such common agents as Lipitor and Zocor. These are all factors that need to be taken into consideration before starting treatment.

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Estrogen

One of the earliest treatments for prostate cancer involved giving men estrogen, the female sex hormone. In fact, doctors were already using it by the 1950s. At that time, estrogenic agents like diethylstilbestrol (DES) were administered orally and clearly caused major responses. Researchers thought that these drugs caused responses because they reduced testosterone blood levels, but the truth is a little more complicated. While estrogenic drugs do suppress testosterone levels, they also directly kill prostate cancer cells by binding to estrogen receptor beta in these cancer cells. Thus, estrogenic drugs can be very effective in men who no longer respond to testosterone blockage. This form of treatment fell out of favor because a randomized controlled trial showed that oral estrogens caused severe cardiovascular side effects that killed almost as many men as they saved.

These side effects include high blood pressure, fluid retention, blood clot formation in the legs, and pulmonary embolism. Recently, several investigators noted that modern cardiovascular disease management allows many of the side effects of oral estrogenic drugs like DES to be safely resolved. For example, we now have diuretics that reduce fluid retention and antihypertensives that reduce blood pressure. Even low dose coumadin can effectively reduce blood clot risk. We also now have a better understanding of how estrogenic drugs work.

But there's also a major controversy surrounding which form of estrogen to use and how to best administer it. As I mentioned, the traditional approach is to give oral estrogenic drugs such as DES. Transdermal estradiol has been extensively studied in women, where it appears to have many advantages over oral estrogen. Compared with the oral route, there is no first-pass exposure to the liver and this reduces liver production of clotting factors, thereby reducing blood clot risk. There are numerous other advantages (Table 1).

Table 1. Transdermal versus Oral Estrogen

Liver Protein Target	Adverse Effect	Oral	Transdermal
Angiotensin precursor	Salt retention Hypertension	Increase	No increase
C-reactive protein	Arteriosclerosis Stroke	Increase	No increase
Suppress IGF1	Muscle loss	Exacerbate	No effect
Clotting proteins Pulmonary Embolism	Blood clots	Increase	No increase

Transdermal estradiol may be the best way to administer estrogenic drugs to men with prostate cancer. A recent clinical study published by Ockrim, et al, in *Journal of Urology* confirmed that transdermal estradiol is a safe and effective way to administer estradiol to men with prostate cancer and can cause very significant anticancer activity. It certainly appears to be safer than oral estrogenic drugs such as DES.

Transdermal estradiol may be the best way to administer estrogenic drugs to men with prostate cancer.

But there are a number of issues that remain to be defined. For example, how many estrogen skin patches are needed to get the best response? Is transdermal estrogen the best way to give estrogen? Or might it be better to inject a slow release form of estrogen? (These are, in fact, available and may prove much more convenient than the skin patch.)

We also use transdermal estradiol to suppress hot flashes: 25 mcg of estrogen is often sufficient to reduce hot flashes and will often cause only minor breast symptoms.

A final advantage of transdermal estrogen is that it is much less expensive than any other form of hormonal therapy.

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Sandostatin

Sandostatin suppresses growth hormone production and is therefore usually used to treat people with acromegaly, a disease caused by too much growth hormone in adults, and gigantism, a disease caused by too much growth factor in children. Around the globe, there are several different antigrowth hormone drugs on the market, but in the United States, only Sandostatin is available. Throughout the rest of this section, I will discuss the drugs in this family as if they are interchangeable, which I believe to be the case.

Growth hormone plays a potential role in how hormone resistance develops. Growth hormone causes another hormone to be released—insulin like growth factor I or IGF1. As many of you probably already know, IGF1 plays a very important role in prostate cancer biology. First, it triggers a major survival pathway for prostate cancer by activating a protein called akt. Akt is important because, once activated, it causes many changes in the cancer cell that make it much more resistant to hormonal therapy, chemotherapy, and radiation therapy. IGF1 also activates pathways that may cause the androgen receptor to function at the low levels of testosterone seen in men who are medically and surgically castrated. So there's actually a possibility that simply suppressing growth hormone could reverse hormone resistance. But this is not a new idea and it has been around since the early 1990s. But it's difficult to identify the right way to use this information and how to best design appropriate clinical trials to test the concept.

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To my mind, the investigators at the University of Athens Department of Urology have done the most convincing work in this regard. In a series of papers, they show that Sandostatin-like drugs, when combined with a steroid called dexamethasone, appear to restore hormone sensitivity to hormone resistant men. This led to a randomized controlled trial that compared chemotherapy with a Sandostatin-like drug + dexamethasone that found the Sandostatin-like combination as effective as chemotherapy in terms of response rate, response duration, and ultimate survival.

Of course, Sandostatin is much less toxic than chemotherapy: about the only side effect is diarrhea during the first month of treatment and mild fatigue. To date, I've had limited experience with the University of Athens protocol, but their results are favorable enough to convince me that this is an important addition to our treatment tool box. I'm now working hard to convince Medicare to pay for it and am optimistic that I'll ultimately be successful.

Leukine

Leukine is the brand name for the hormone GM-CSF, or granulocyte macrophage colony-stimulating factor. Leukine is interesting because this is a hormonal treatment for prostate cancer that has nothing to do with testosterone. The major defense against infection involves activating the white cells in the blood. These white cells include a wide range of different cell types that act together to fight off viral, bacterial, and fungal infections. These same cells also appear to play a role in the immune response to cancer cells. GM-CSF stimulates a wide range of white cells involved in the defense against infection and antitumor immunity. It does this by increasing the number of white cells as well as their biologic activity. Leukine is approved for use with chemotherapy to prevent infections. Physicians also use it in patients whose bone marrow transplants have not taken well because it can lessen the risk of infection.

While Leukine, or GM-CSF, is normally used to reverse low white blood counts caused by chemotherapy, it also improves host immune response to cancer. Experimentally, it has been used to enhance cancer vaccines' ability to generate a therapeutically effective response. It is also used to expand dendritic cells used by cancer vaccines, such as the Provenge vaccine developed by Dendreon. Clinically, subcutaneous Leukine administration can cause responses in melanoma. With this background in mind, Eric Small

(Rini, et al) at UCSF reports his experiences using Leukine to treat a group of advanced prostate cancer patients. In a paper published in *Journal of Clinical Oncology* this year, Small reported that Leukine could slow or even arrest prostate cancer progression. The schedule used in Small's study was every day for 14 days out of every 28. Since the study's publication, I've treated a number of patients with Leukine and have pretty much confirmed what Dr. Small reports. Furthermore, patients tolerate this treatment quite well. That said, patients can also get a transient inflammatory reaction at the injection sites as well as edema. But both side effects reverse within 72 hours if we stop drug administration. Over the counter antihistamines, such as Claritin, are quite effective in lessening the severity of these side effects.

Leukine also appears to have useful activities far beyond infection and cancer immunity. A recent study in Crohn's disease suggests that the 14 day schedule may not be optimal: patients treated daily for 8 weeks had side effects comparable to that seen in the 14 day schedule. Finally, I should mention that Leukine has a number of other interesting therapeutic effects, including reversing damage to the gastrointestinal tract caused by radiation and chemotherapy and the reversal of coronary artery disease.

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Combination Therapy

Since ketoconazole, estrogen, Leukine, and Sandostatin each attack the prostate cancer cell in a different way, it is possible that these agents might be used in combination with each other or with other agents used to treat prostate cancer. Since these agents have very different side effects, it is also possible that patients will tolerate combinations of these agents quite well. We are only beginning to see clinical trials testing such combinations. For example, Eric Small presented an abstract at this year's ASCO that tested ketoconazole + Leukine and found the combination resulted in a response rate of 78% and was well tolerated. I have also repeatedly used ketoconazole and transdermal estradiol together and found them very effective in hormone resistant prostate cancer, even after chemotherapy has failed. Patients also tolerated it very well. Adding Sandostatin (because it blocks a major survival pathway for prostate cancer) may increase the response to many other agents that act to kill prostate cancer, including ketoconazole and estradiol as well as chemotherapy. Such uses represent an important area for future study.

Case Study: XD

XD's case nicely illustrates many of the issues that make treating men who have advanced disease at the time of diagnosis so complicated. In the process of trying to get XD into complete remission, my staff and I at the American Institute of Diseases of the Prostate (AIDP) ended up using all of the tools we've discussed in this issue and in Vol 9 #5: aggressive androgen withdrawal, ketoconazole, transdermal estrogen, Leukine, and even taxotere-based chemotherapy. But don't look at this case as a road map for your own treatment: at AIDP we individualize each treatment path to fit a patient's specific overall medical condition.

For example, XD had significant arteriosclerosis leading to the placement of stents in his coronary arteries right in the middle of prostate cancer treatment. This altered my approach and from that point onward we had to adapt to the aggressive heart treatment recommended by his cardiologist.

In September 2003, XD made an appointment with his urologist when he began to have symptoms of urinary tract obstruction. The urologist quickly noted that XD's prostate was abnormally enlarged and subsequently checked his PSA, which proved to be 1,026 ng/ml. Transrectal ultrasound and biopsy of the prostate gland revealed a Gleason 4+4=8 prostate cancer that involved both sides of the gland. A CT scan showed clear involvement of the lymph nodes along the iliac arteries on both sides of his pelvis and in the nodes along the back of his abdomen. A bone scan showed a hot spot in his left scapula.

We started XD on Zoladex plus 50 mg of Casodex toward the end of August. When I saw him close to three weeks later, his PSA had dropped to 69 ng/ml. I increased his Casodex to 150 mg per day and added Proscar. Thirty days later, his PSA had dropped to 3.7 ng/ml. By December 10, his PSA reached its lowest point (1.42 ng/ml) and then began to increase, indicating failure of initial hormonal therapy. I prescribed ketoconazole, Leukine, and 0.2 mg per day of transdermal Estradiol. By March, his PSA reached 0.76 ng/ml and again began to increase. At this time, he developed chest pain that proved to be secondary to partial blockade of two coronary arteries. We had to stop cancer treatment until these blocked arteries were opened up again using stents. From this time onward, he was also on Plavix and baby aspirin. By the end of April, his PSA had again increased, this time to 1.08 ng/ml. I placed him back on ketoconazole and Leukine and his PSA decreased to 0.4-0.45 and remained in this range. Prior to the onset of XD's cardiac problems, it became clear that we wouldn't attain a complete remission with ketoconazole and Leukine. For this reason, we suggested he go on chemotherapy. He began chemotherapy with Taxotere and high dose Calcitriol.

He didn't respond to this treatment: his PSA increased gradually from 0.40 to 0.62 ng/ml. He'd tolerated taxotere remarkably well, with almost no side effects. (Taxotere is eliminated from the body by a liver protein called CYP3A4 and some people have high levels of this protein, leading to rapid destruction of Taxotere. Interestingly, this same protein appears in prostate cancer cells when they become resistant to taxotere.)

At that point, I switched him to a combination of Taxotere and Navelbine and re-introduced Leukine. Note that I was still concerned about a possible CYP3A4 problem. But a single ketoconazole pill per day can block CYP3A4 without adding any significant risk. For this reason, I put XD on 200 mg of ketoconazole once a day. On this program, his PSA dropped to 0.13 by the end of January 2005, but did not decline further. In February 2005, I decided to stop further chemotherapy. At this point, I increased his Leukine from 250 mcg 14 days out of every 28 to 500 mcgs per day. XD continued taking Zoladex and Proscar. Over a few weeks, his PSA dropped to 0.10-0.11 and remained there until August 2005.

Two years after his diagnosis, I decided to stop hormonal therapy and didn't administer his routine Zoladex shot. He switched from Proscar to Avodart, because his dihydrotestosterone was not as low as I would have liked. He remained on Leukine. Over the next 8 weeks, his PSA dropped to 0.06 ng/ml and has remained there. (To put this PSA in perspective, a successful radical prostatectomy will yield a PSA below 0.04-0.05 ng/ml.) Now that his PSA has dropped to this very low level, we are going to see if we can detect any cancer remaining. He will have a bone scan to look at his left scapula. He will also get a CT scan, preferably at the same time as a Prostatecint scan (See Vol 8 #12, Lymph Node Staging.)

XD's case was a complex path, a journey that must sometimes be taken to attain the best possible cancer response. The next challenge XD and I face is to prevent disease recurrence. We both hope Leukine and Avodart will do the job.