

UCSF Genitourinary Medical Oncology Program
Advanced Prostate Cancer and its Treatment:
An Information Handout for our Patients with Advanced Prostate Cancer
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This handout was developed to provide you with general information about the different treatments available for advanced prostate cancer at UCSF. In general, we define prostate cancer as *advanced* when it requires additional treatment beyond surgery and radiation. Therefore, most of the following treatment options are for patients with metastatic prostate cancer. The term *metastatic* refers to prostate cancer that has spread from the prostate to distant sites, such as bones and lymph nodes. Men who have no visible evidence of cancer at distant sites, but whose PSA is rising may be offered some of these treatments; this condition is known as *rising-PSA* or *PSA-only* prostate cancer. Also, many of the terms below refer to whether or not hormone therapy has been administered, and if it remains effective in controlling the cancer: a person whose disease is responding to hormone therapy is considered to have *hormone-sensitive* prostate cancer, whereas a person whose disease is growing despite hormone therapy is considered to have *hormone-refractory* prostate cancer (despite the term hormone-refractory, it is important to understand that further hormone treatments are a significant part of treatment).

The UCSF Genitourinary Medical Oncology Program has a strong commitment to delivering state of the art care, improving existing treatments, and developing entirely new therapies for men with all stages of prostate cancer. We have an extensive clinical trials program that applies to virtually all patients, but not all patients treated at UCSF participate in these trials, and participation in clinical trials is not necessary to receive care at UCSF. This handout briefly describes both standard and investigational treatments for prostate cancer; we will provide considerably more information about specific treatment options during your visit. The specific treatment options available to you will depend on the treatments you have already received and on your current medical condition.

HORMONE THERAPY

Hormone therapy is frequently the first treatment offered for patients with metastatic prostate cancer; it is also an option for some patients who choose not to have surgery or radiation for cancer that is confined to the prostate, and for some patients with a rising PSA after surgery and/or radiation. The male hormone *testosterone* causes the growth of prostate cancer, and reducing testosterone levels in the body with hormone therapy can kill prostate cancer cells. Testosterone is primarily produced by the testicles, with a small supply made by the adrenal glands. Hormone therapy, otherwise known as *androgen deprivation therapy*, refers to treatments that reduced the amount of testosterone.

There are two treatment options that reduce the supply of testosterone from the testicles. One method is to remove the testicles surgically, known as *orchiectomy*. The other option is to start medications that stop the

production of testosterone from the testicles. These include leuprolide (injection: Lupron[®]; implantable: Viadur[®]; subcutaneous: Eligard[®]), goserelin (Zoladex[®]), or degarelix (Firmagon[®]). These medications are as effective as orchiectomy in reducing testosterone levels and treating prostate cancer. Side effects of both surgery and the medications can include hot flashes, low sexual desire and impotence, fatigue, mood changes, muscle loss, weight gain, anemia, and in some patients on long term therapy, *osteoporosis* (thinning of the bone). There may be an increased risk of heart disease and diabetes. To maintain bone health, we recommend that all patients on hormone therapy take calcium (500-1000 mg/day) and vitamin D (400 IU/day), and participate in weight-bearing exercise regularly (which also helps to maintain muscle tone and reduce fatigue). We also recommend aerobic exercise to maintain cardiovascular health. The impact that hormone therapies have on an individual's sex life is equally as important as the other side effects, and we hope to provide an open, supportive environment for you to discuss this if you wish; we can also refer you to our urology program for the treatment of erectile dysfunction.

Additionally, you may also be started on an oral medication called an *antiandrogen*, which includes flutamide (Eulexin[®]), bicalutamide (Casodex[®]), or nilutamide (Nilandron[®]). These medicines block the effects of testosterone, regardless of where the testosterone is produced (testicles or adrenal glands), which can further treat prostate cancer. Most physicians who treat prostate cancer feel that these medications are equivalent to one another. Antiandrogens can make blood tests that measure liver function abnormally high, and on rare occasions may need to be stopped because of this; the liver function tests return to normal in the vast majority of patients once the drug is stopped. Therefore, we recommend checking liver tests regularly after starting any of the antiandrogen pills. Flutamide may cause mild stomach distress and diarrhea. Nilutamide can decrease the ability of the eyes to adjust to changes in light (e.g. going from daylight into a dark room) and it can make you feel sick if you are drinking alcohol. It rarely results in shortness of breath (stop the drug immediately and call us if it does).

There are alternative ways of administering hormone therapy. While many patients stay on androgen deprivation therapy continuously, some patients are treated with *intermittent* therapy. This involves an injection every 3 months with or without an antiandrogen pill, until the PSA falls to its lowest point and for a total of 9 to 12 months. The drugs are then stopped, followed by careful PSA monitoring (usually every 1 to 3 months). When the PSA rises to a level predetermined by you and your oncologist, the medications are started again for 9-12 months at which point they are stopped and the PSA allowed to rise again, and so on. The benefit to this approach is that you will be off hormone therapy for a period of time during which you may experience less side effects. There are also ways of treating prostate cancer that do not involve lowering of testosterone, known as *peripheral androgen blockade*. You can discuss with your provider if you are a candidate for either of these treatment strategies. In addition to these types of traditional hormone therapies, we have clinical trials ongoing for patients who have PSA-only disease including: 1) one study utilizing a novel hormonal agent, an

antiandrogen called **ARN-509**, and 2) a second study testing the use of an anti-fungal medication **itraconazole** that has shown activity in patients with more advanced prostate cancer.

THE NEXT STEP AFTER HORMONE THERAPY: ANTIANDROGEN DISCONTINUATION

If PSA rises despite the combined use of testosterone-lowering injections and antiandrogen pills, the next step is to stop the antiandrogen pills. While these medications may be effective initially in slowing the growth of prostate cancer, after a period of time antiandrogens may add fuel to the fire and feed the cancer. For this reason, approximately 10-15% of patients will have an improvement in their disease when the antiandrogen pill is stopped. HOWEVER, LUPRON, ZOLADEX, or ELIGARD SHOULD NEVER BE STOPPED. In order to determine if you are having a response to antiandrogen discontinuation, PSA will be checked when you stop taking the antiandrogen and every 4 weeks thereafter. If your PSA declines or remains stable, no further treatment is undertaken until the PSA rises again. Responses to antiandrogen discontinuation last an average of 5 months, but it can last for several years in some patients.

HORMONE-REFRACTORY PROSTATE CANCER: AFTER ANTIANDROGEN DISCONTINUATION

If PSA continues to rise and/or tumors continue to grow after stopping flutamide, bicalutamide, or nilutamide, subsequent treatment options depend on the characteristics of the disease. There are four general categories of treatment that can be considered, which will be described briefly below; your provider will discuss with you the relative benefits and side effects of the treatments that are best medically suited for you, and provide you with additional written information. Some of our therapies are investigational in nature; hence, there may be restrictions placed by the National Cancer Institute, the FDA, or the trial sponsor, on situations in which a particular treatment can and cannot be used.

1. Additional Hormone Therapy:

Sequential use of antiandrogens: =

Approximately 20-40% of patients whose cancer has worsened on one of the antiandrogens may benefit from trying another one of these drugs. While changing from one antiandrogen to another may provide benefit, an antiandrogen that has stopped working in the past should not be reused. *Enzalutamide (Xtandi®)* is one of the newest antiandrogen therapies, and it blocks the effects of testosterone on prostate cancer cells even in patients who have developed resistance to the other antiandrogens. In men who had previously received chemotherapy, enzalutamide has been FDA approved due to its ability to improve survival, shrink tumors, and induce PSA responses in 30% of patients. Studies in patients who have not previously received chemotherapy are ongoing. The drug is taken daily by mouth (with or without prednisone) and is well tolerated. There were rare reports of seizures in men treated with enzalutamide, so please discuss any prior history of seizures with your healthcare provider.

Adrenolytic therapy:

Ketoconazole (Nizoral®) is a form of hormone therapy which works by shutting down testosterone production by the adrenal glands. Approximately 50-60% of patients will experience benefit from this therapy. Side effects include nausea, liver function test abnormalities, and mild fatigue; these will resolve if the drug is discontinued. Rarely, patients develop rashes. In addition to making testosterone, the adrenal glands balance minerals and fluids in the body by producing the hormone hydrocortisone. For this reason, all patients on ketoconazole will also receive hydrocortisone pills to replace what the body normally produces. Certain cholesterol medications (statins) can cause serious drug interactions when taken with ketoconazole. If you are on a statin, please speak to your healthcare provider about alternative cholesterol medications that can be used safely.

Abiraterone acetate (Zytiga®) shuts down hormone production in the adrenal gland like ketoconazole. It is taken orally once daily in conjunction with prednisone taken twice daily. For men whose cancers have or have not already been treated with chemotherapy, abiraterone has been FDA approved due to its ability to improve survival, shrink tumors, and induce significant PSA declines in 30-60% of patients. Abiraterone is generally very well tolerated. Side effects include increased blood pressure and fluid retention that is prevented by the use of prednisone.

2. Chemotherapy:

Chemotherapy refers to drugs that directly kill prostate cancer cells. Usually, these medicines are given intravenously in our infusion clinic.

Docetaxel (Taxotere®) is a chemotherapy given intravenously every 3 weeks in conjunction with prednisone taken twice daily. The combination of docetaxel and prednisone was FDA approved due to its ability to prolong survival in men with metastatic, hormone-refractory prostate cancer. Approximately 50-60% of men treated with docetaxel will have a significant decrease in PSA, and 20-40% will have shrinkage of measurable tumors. Side effects include neuropathy (nerve damage that usually occurs after many doses, typically described by patients as numbness or tingling in the fingers and toes), fatigue, fluid retention, and nausea.

Cabazitaxel (Jevtana®) is a chemotherapy option for men who have already received docetaxel. Like docetaxel, cabazitaxel is given every 3 weeks in conjunction with prednisone taken twice daily. Cabazitaxel received FDA-approval for the treatment of metastatic hormone-refractory prostate cancer in men who have already received docetaxel, due to its ability to improve survival. Major side effects are diarrhea, low blood counts, and impairment of the immune system that may put you at risk for serious infections. Due to the risk of infection during the time when you are neutropenic (when your white blood cell count is low, usually 7-10 days after receiving cabazitaxel), cabazitaxel should be given with an injection called Neulasta® that can boost the immune system.

There are other chemotherapeutic options than can be used after (sometimes in combination with) docetaxel and cabazitaxel, such as carboplatin and mitoxantrone, They can be effective in some patients by easing pain and shrinking tumors. Your care provider will discuss these options if they are medically suited for you.

3. Vaccine Therapy:

These agents have the potential of stimulating your immune system to fight prostate cancer.

Sipuleucel-T (Provenge®) is a vaccine that stimulates your immune system to fight against prostate cancer. Sipuleucel-T is custom-made for each patient: first, patients have their blood run through a machine in an outpatient pheresis center for 2-3 hours in order to extract immune cells; second, these cells are mixed in an incubator with an immune stimulant plus a protein that is commonly found on prostate cancer cells; finally, this sipuleucel-T product (Provenge) is returned to the patient in a 1-hour infusion, given 72 hours days after the immune cells are extracted. The whole process is repeated every 2 weeks for a total of 3 doses. Sipuleucel-T alerts your immune system that prostate cancer cells should be attacked as if they were foreign invaders. In clinical trials in men with metastatic hormone refractory prostate cancer, those who received sipuleucel-T lived longer than those who did not. Sipuleucel-T does not cause immediate PSA declines or shrink tumor like other medications but it may make the body better able to fight prostate cancer over time and make subsequent cancer therapies more effective. Side effects overall are mild, including flu-like symptoms that resolve within 24-48 hours, and rarely, allergic reactions at the time of infusion which are treatable.

4. Investigational Therapies:

There are many opportunities to participate in clinical trials at UCSF. Some of the clinical trials include investigational agents, while others include the FDA-approved therapies described above, using them in novel ways or in combination with investigational agents. For example, at UCSF, **abiraterone** is being investigated in multiple settings:

- In patients who have previously been treated with ketoconazole
- In combination with **sipuleucel-T (Provenge®)**, a vaccine therapy
- In patients with non-metastatic disease, to see if it can delay the onset of metastatic disease
- In combination with **BEZ-235**, an investigational drug that blocks a cancer growth pathway
- In combination with **cabazitaxel**, an effective chemotherapy for advanced prostate cancer
- By increasing the dose of abiraterone beyond the current FDA-approved standard dose when patients become resistant to standard dose abiraterone

Other investigational trials include:

- **ARN-509**: a new antiandrogen (like enzalutamide) shows activity in men with hormone-refractory prostate cancer; at UCSF, a study using ARN-509 instead of, or in combination with standard hormone therapy in patients with PSA-only prostate cancer is ongoing
- **Orteronel**: a hormone therapy that shuts down hormone production in the adrenal gland (like abiraterone and ketoconazole). Studies are ongoing in men both with and without metastatic disease
- **Cabazitaxel-based therapy**: The *CaMP* study (**Cabazitaxel plus Mitoxantrone and Prednisone**) will test whether to combination of cabazitaxel and mitoxantrone with prednisone is effective and safe for patients with hormone refractory prostate cancer who have never previously received chemotherapy.

Another study tests the combination of **cabazitaxel and abiraterone** in patients with hormone-refractory prostate cancer who have never previously received chemotherapy.

In general, most clinical trials require that your prostate cancer is worsening to be eligible. If you are responding to a particular treatment, participation in a clinical trial might not be possible at the present time, but may be appropriate in the future. We have an extensive clinical trials program, and your care provider will discuss any trials for which you may be eligible.

Additionally, UCSF has an active and growing **Phase I/Developmental Therapeutics** program led by an experienced multidisciplinary team. In general, phase I trials evaluate the safety of new pharmaceutical compounds in a small number of patients. If you participate in a phase I trial, you will see an oncologist that specialized in phase I trials in conjunction with your current oncologist. The types of drugs available are variable in how they work on tumors. You can ask your GU Medical Oncologist for more information at any time.

OTHER THERAPIES

Bone supportive treatment:

Zoledronic acid (Zometa[®]) and denosumab (XGEVA[®]) are medications that are used to prevent thinning of the bones. They have also been shown to reduce the rate of bone-related events (e.g. fractures, bone pain, need for radiation therapy) in patients with hormone refractory prostate cancer who have bone metastases. Zometa is given by vein every 3-4 weeks by a 15-30 minute infusion. Side effects of Zometa include kidney damage (we check your kidney function with a blood test before every dose) and flu-like symptoms. XGEVA is given by subcutaneous injection monthly. XGEVA can lower calcium and phosphorus levels in your blood, so these must be checked before each dose. Both Zometa and XGEVA should be taken in combination with a calcium and vitamin D supplement.

Both Zometa and XGEVA can rarely cause a condition called *osteonecrosis*, or bone damage, of the jaw. If you are currently undergoing or planning dental work (routine cleaning is ok), please discuss this with your care provider.

Please note that this is a very general information sheet. We will be providing you with more information as we discuss the treatment options that are best medically suited for you. Our primary commitment is your well-being. Please let us know if there is more information that you need. Should you have any additional questions, please feel free to contact us at 415-353-7171. Our webpage has updated listings of clinical trials and other materials of interest, and can be accessed at <http://cc.ucsf.edu/trials> (type in keywords: **prostate cancer**).