RECURRENT PROSTATE CANCER

A Working Document for Men with

Recurrent Prostate Cancer

By Joel T Nowak, M.A., M.S.W.

Director of Advocacy & Advanced Prostate Cancer Programs for Malecare

Edited by Wendy A Lebowitz, M.P.H., Ph.D.

Senior Psychologist, Interfaith Hospital, Brooklyn, N.Y. & Malecare

Version 1.0.0 (check at http://www.malecare.org/advanced-prostate-cancer-program/ for updates.

Malecare is our country's leading prostate cancer support and advocacy nonprofit organization. This booklet has been prepared to help you understand more about recurrent prostate cancer. Most all men feel shocked, scared and betrayed when they are told that their prostate cancer has returned to threaten their lives. This booklet is set to arm you with sufficient knowledge to join with your doctors in fighting the prostate cancer inside you. In two hours or less, after reading Malecare's recurrent prostate cancer document, you will know more than enough to ask focused and life-saving questions about your cancer. You will feel stronger than you feel now, and you will feel more confident in fighting for your life.
This document does not advise you about the best treatment for you. That's where your work with your doctors comes in. Do not use any of the information in this document without first consulting with your doctor and other relevant health care providers. This document will be updated as needed, and, assuming you registered at malecare.org's advanced prostate cancer program, you should receive notices about updates. Please email your comments about this document to me darryl@malecare.org, we promise to continue to focus on your needs.
To your health!

Darryl Mitteldorf, LCSW
Executive Director
Malecare

Introduction

You've been diagnosed with prostate cancer and have struggled through treatment choice making and side effects. You hoped that your prostate cancer was put to rest.

Today, you find yourself with a rising PSA. Your prostate cancer is threatening your life, again.

It doesn't seem fair, but this will happen to about 30% of us who have been treated for prostate cancer. Even though our doctors told us that our treatment worked and we were free of cancer, it's back. Truth is, our prostate cancer never left us. The initial treatment simply failed to remove or destroy all of the cancer cells. No one is at fault. Just the nature of the beast and the current state of medical science

Recurrent prostate cancer is usually discovered by a rising PSA. However, in more advanced stages it can be accompanied by stiffness in your lower back, upper thighs or hips. Some men feel aches and pains in their bones, the most common site for the development of prostate cancer tumors. In advanced stages you could have swelling in your ankles (edema) caused by obstructions in your blood vessels or lymphatic system, weight loss, and a loss of red blood cells (anemia).

Recurrent prostate cancer is serious, but there are excellent treatments and many emerging treatments are on the horizon. Many of us live long, fulfilling and happy lives with this disease, even after it has recurred!

To successfully deal with this kind of prostate cancer, take an active role in deciding about your personal care, stay healthy by exercising and eating well and learn to use your friends, family and support groups to improve the overall quality of your life.

You already are doing the right thing, by reading this document….read it all. We will help you understand *your* disease. And, you will have new and better ideas on managing your prostate cancer.

About Fighting Recurrent Advanced Prostate Cancer

Every man has a different experience of their cancer. Our bodies are different. Even the shape and the size of our prostates – when we had them – were as unique as snowflakes. Each of us responds to treatments indifferent ways, too. As you progress through your new treatments, consider three ideas: listen to your body, understand what makes you happy, and decide how you want to live your life- these are the lenses you will need to view your treatment choice making from here on out.

What You Can Do, Starting Today.

Troll the internet. Ask or email questions of other men battling the disease and find doctors you trust who have experience treating men with recurrent prostate cancer. You may not be a scientist or a

doctor, but you can ask questions and look critically at everything you read and hear. Learn to read and evaluate research. You decide what you will believe and what not to believe.

A good, "heart healthy" diet and regular exercise will not only help extend your life, but it will also mitigate side effects from treatment. Make your life better, feel better and enjoy yourself to the fullest.

Work with a nutritionist if possible. Limit your consumption of red meat, dairy products and sugar. Consider purchasing only organic vegetables and fruits and eat a lot of them.

Find and talk with other men who have prostate cancer, ideally men with recurrent and advanced prostate cancer. If you can, find a face-to-face support group. Ask your doctor or the nurse if they know of any support groups you could join. Malecare sponsors an on-line support group for men with advanced prostate cancer and their care givers. Currently, we have over 560 participants from many different countries. To join, go to:
http://health.groups.yahoo.com/group/advancedprostatecancer/join.

Your Medical Records

Your medical records belong to you, including a record of every visit to the doctor as well as every test and scan you have ever had. If you haven't already gathered together these records you must do so, today. Ask your doctor, the nurse or the office staff to give you a copy of all of your records. Blood tests, progress notes, scans, etc. Expect to pay a small duplication fee… it could be the best money you spend.

Keep all these records in chronological order. If you go to a new doctor copy the entire contents of your medical history file and give it to the doctor, ideally before your first appointment. Most doctors will want to see these records, sometimes before they will even agree to set up an appointment. By personally supplying the records you will know that the doctor has received them, in a very timely manner.

Each time you have a new blood test, an appointment with a doctor or a scan, get a copy of the results and add them to your personal medical history file. Make sure that you send all of your doctors a copy of every test and scan as soon as you receive them yourself. Don't assume that your doctor already has a copy.

Make a graph of your PSA scores and keep it up-dated. Observe the slope and changes in the PSA scores and calculate your PSA velocity and doubling time. You can go to the web site at Memorial Sloane Kettering Hospital in New York City to calculate and graph your changes in your PSA measurements:
http://www.mskcc.org/applications/nomograms/Prostate/PsaDoublingTime.aspx

Try to understand everything in your records. Ask your doctor to explain anything in the record that you don't understand. After your doctor explains something, if you still do not understand, ask again. Keep asking until you do understand. From now on, you are the boss of your health.

The Role of PSA in Men with Prostate Cancer

PSA is not a good measure of prostate cancer before a man is diagnosed; however, once he has been diagnosed and received a primary treatment the PSA test becomes your best available and the most reliable measure of your cancer's progress. Always know your PSA. We recommend that at the minimum you have a PSA test every three (3) months. Plot your PSA on a graph so that you can see changes in trends. Calculate and know your PSA velocity and your PSA doubling time by graphing the scores at: http://www.mskcc.org/applications/nomograms/Prostate/PsaDoublingTime.aspx

When Are You Considered to Have A Prostate Cancer Reoccurrence?

If you have been treated with any primary treatment type (surgery, radiation, HIFU etc.) for prostate cancer and your PSA has again started to rise, under certain definitions, you are said to have recurrent prostate cancer. This means that your cancer has returned and has again started to grow.

The medical profession has developed very specific definitions as to when you have experienced a prostate cancer reoccurrence.

You are considered to have recurrent prostate cancer if you had received any type of radiation as your primary treatment and:

1- The ASTRO Definition- You have three (3) consecutive rises in your PSA score after having reached your nadir* score.

2- The PHOENIX Definition- Once reaching your nadir* score, if your PSA increases by 2.0 you are assumed to have had a reoccurrence. (If your nadir* is 1.2, then if your PSA becomes 3.2 or more you have experienced a reoccurrence).

**Nadir – Is your lowest PSA achieved post radiation. Because it can take a long time for radiation to work it can take up to 18 months to achieve a stabile PSA nadir. A longer period of PSA fall and a lower PSA nadir predicts a higher of being in that 1/3 number of men who have a prostate cancer recurrence.*

You are considered to have recurrent prostate cancer if you had any type of surgery as your primary treatment and:

3- AUA Definition- Your PSA increases to a level greater than 0.2 and continues to increase confirmed by at least one additional PSA test over the 0.2 threshold, you are assumed to have had a reoccurrence. The ideal for PSA scores after any surgery is for it to become undetectable.

CAUTION- A post on the advanced prostate cancer blog: (http://advancedprostatecancer.net/?p=1900) warns that there are medications that are commonly taken that will alter your PSA and perhaps interfere with your ability to accurately monitor your PSA for a recurrence. Men taking NSAIDS, statins and thiazide diuretics will have a reduced PSA score by clinically relevant amounts. The impact of these drugs on monitoring PSA levels in unknown)*Reference: J Clin Oncol. 2010 Aug 2. Epub ahead of print. doi: 10.1200/JCO.2009.27.9406 ; Chang SL, Harshman LC, Presti JC Jr; PubMed Abstract, PMID: 20679596)*

What is a Prostate Cancer Recurrence?

We have described the way doctors can diagnosis a prostate cancer reoccurrence, but what is actually happening in my body when I have a prostate cancer recurrence?

When you were initially treated for prostate cancer the doctors treated you on the assumption that all the cancer was still entirely within your prostate gland. Before treatment, you had various scans which did not show that there were any signs of the cancer anywhere other than in your prostate gland itself. Scanning technology is limited and scans are not able to detect lone cancer cells or very small tumors. If you have already had a release of cancer cells from the gland they could circulate through your body and either not grow or grow very slowly. At some point the cancer starts to grow and again generate PSA, even though you have been previously treated. It is this PSA that is detected and which is used to diagnosis the reoccurrence.

What Should Happen If My PSA Starts Rising?

If your PSA begins to rise and falls into one of the categories described as defining a prostate cancer recurrence, your most likely next step would be to have a series of scans to determine if you have developed any identifiable metastases (tumors). The possible scans that will be recommended are: a bone scan, an MRI, a PET scan and a CT scan. There is a complete description of each of these scans later in this document.

What is a PSA Only or a Biochemical Reoccurrence?

It is not uncommon for all your scans to come back negative, meaning there wasn't any tumors visible on the scans, but your PSA is still rising. This is called a PSA only (biochemical) reoccurrence. Sometimes

men in this situation are said to have micro-metastatic prostate cancer or bio-chemical reoccurrences. The normal course of a biochemical reoccurrence is the development of metastases that will eventually become visible on scans.

What is a Metastasis?

A metastasis, or a met, is a tumor, or an abnormal growth, that has developed in another part of the body other than from where the original cancer had started. We do not know how metastases spread from one part of the body to another. Some scientists theorize that the cancer moves through the blood stream while others think it travels through the lymph system. No matter how it travels, the most common site for prostate cancer metastasis is the bones, particularly the bones in the pelvis, spine, thighs and ribs. Prostate cancer also travels to soft tissue organs such as lymph nodes, the liver, lung and brain. Over time the mets will continue to grow, breaking bones and eventually pushing aside surrounding organs causing pain, disability and eventual organ failure.

If you begin to experience unusual pains, or even aches that persist, tell your doctor as you might have developed a met which might need treatment.

When you first have a PSA recurrence and then on an as needed basis, your doctor will arrange for you to have various scans to evaluate your status. To determine if you have a bone metastasis your doctor will recommend either an x-ray (not very effective) or a bone scan.

What Is A Bone Scan?

A bone scan is performed by injecting intravenously (IV) a small amount of a radioactive marker into your arm. Three hours after the IV you will lie on a table that will slowly move you through a scanner which will record any bones that have a high turnover or concentration of the marker. Bone scans are painless and do not place you into a tube where you might feel uncomfortable.

Bone scans are highly sensitive and pick up infections and very small bone fractures, as well as tumors. Since they cannot discriminate between a tumor, an infection, or a break, a CT Scan, PET Scan or MRI will be needed to better characterize the lesion.

What Is An MRI

An MRI is a non-invasive method of scanning soft tissue. It uses only magnetic and radio waves so there is no exposure to any form of radiation.

To perform the scan you will lie on a movable table that will slide into a cylindrical tube which is actually a large magnet. Once you are inside, magnetic radio waves that are between 10,000 to 30,000 times stronger than the magnetic field of the earth are sent through your body. These waves force the nuclei in your body's cells into a different position. As they move back into their normal position they send out radio waves of their own which a computer uses to generate a picture.

A MRI is capable of creating pictures of almost all the tissue in your body as well as tissue that is surrounded by bone, allowing for even the tissue in your skull and spinal column to be visualized by your doctor.

A MRI can also use contrast agents to highlight an organ or specific tissue. Sometimes the contrast material is called dye.

What Is A CT Scan?

A CT Scan or Computed Tomography, also known as Computed Axial Tomography (CAT Scan), is another painless method used to scan your body when trying to decide if you have developed any metastases. CT Scans are a sophisticated x-ray procedure where there are multiple images taken in cross sectional "slices" which are compiled by a computer. The scan produces a picture of soft tissue, blood vessels and bone.

Although considered safe, CT Scans do use radiation which might increase your risk for the development of another primary cancer.

Like MRIs, CT Scans can also use contrast agents to highlight an organ or specific tissue. Sometimes the contrast material is called dye.

What are the Significant Differences between an MRI and a CT Scan?

An MRI allows the doctors to take pictures from any angle while a CT Scan allows only a single horizontal view. MRIs do not use any radiation and they yield more detailed "pictures."

What is a PET Scan?

A positron emission tomography (PET) scan is an imaging test that helps doctors see how the organs and tissues inside your body are actually functioning.

The test involves injecting a small amount of a radioactive material, called a radiotracer, into a vein of your arm. The tracer is absorbed by your organs and tissues. You will then lie down on an examination table that is moved into a doughnut-like shaped machine. This machine detects and records the energy

given off by the tracer substance and, with the aid of a computer; this energy is converted into three-dimensional pictures.

Many modern machines combine a PET scan with a CT to get the best possible view of your internal functionings.

Your Doctor – Who Should It Be?

Most of us are under the treatment of an urologist when we are diagnosed with prostate cancer. We usually remain under the care of this doctor through our primary treatment and then our follow-up PSA monitoring. We at Malecare firmly believe that if you experience any sort of reoccurrence, or become suspicious that you are having a reoccurrence of your prostate cancer, you should seek the care of a medical oncologist, especially one who treats large numbers of men with recurrent prostate cancer or a urologist who specializes in treating men with recurrent advanced prostate cancer. We do not believe that a general Urologist can give you the beast level of care.

Always consider having a second opinion. A lot of medicine is subjective and different doctors can have different views when reviewing your case. Seek a second opinion from a doctor who is from a different medical practice and at a different institution. Certain institutions develop specific protocols that they follow despite the individual nature of your disease. Remember, you and your disease is different from the next mans. Protocols have a valuable place in medicine, but as a starting off point, not as a bible on how to treat a disease.

What Types of Treatments Are Appropriate?

Recurrent prostate cancer is cancer that, in most cases, has left the prostate gland and spread to some other part of your body, be it bones or soft tissue. Sometimes labels can be confusing because recurrent prostate cancer is also referred as advanced prostate cancer or even metastatic prostate cancer. Prostate cancer that is no longer confined to the prostate gland, as in most incidents of recurrent prostate cancer, need to be treated with systematic treatments, treatments affect the entire body, not just a targeted localized area.

The only exceptions are if you still have a prostate gland after treatment (as you do if you have received radiation, seeds or HIFU) and the PSA rise is due only to some cancer cells that remain active in your gland, additional treatment to the gland can help; or if you have some prostate cancer cells remaining only in the area immediately proximal to where the gland had been prior to surgery. For all practical purposes, when you do have a recurrence, you should operate as if you have advanced prostate cancer, or cancer that is now systemic and your treatment needs to be a systemic treatment.

Curing Recurrent Prostate Cancer

Localized prostate cancer is curable by any number of treatments, including radiation (seeds and external beam radiation), surgery (open, laparoscopic and robotic assisted) , high intensity ultra-sound (HIFU) and cyrotherapy.

Recurrent prostate cancer, when caught very early after failed primary treatment, is sometimes curable, but it must be caught very early in its progression. If the primary treatment you had was surgery and your PSA begins to rise, or if it does not become undetectable after surgery, starting a salvage therapy prior to the PSA achieving a score of 1.0 might still beat the cancer and provide you with a "cure".

When you do not catch post surgical reoccurrence prior to a PSA score of 1.0 the cancer should not be considered curable. However, there are many available treatments that will slow down the progress of the cancer, reduce symptoms and extend your life for many years. The goal of treatment is to turn your recurrent prostate cancer into a chronic illness.

Living with Recurrent Prostate Cancer

Most men with recurrent prostate cancer can live for many healthy years while experiencing an excellent quality of life (QOL). The trick to living a healthy and happy extended life is to learn as much as possible about this disease, work hand-in-hand with your doctors in shaping your treatments, be flexible in your treatment decisions, advocate for yourself and always give yourself reasons to enjoy your life.

Living with recurrent prostate cancer we all will become more aware of our own mortality. Being aware of the possibility of our death, we become more introspective about our life and its value. It is very common for men with recurrent prostate cancer to think about how they want their life to be conducted, what is important to them, how they wish to be remembered and what impact on the world they wish to leave.

On Malecare's advanced prostate cancer blog (www.advancedprostatecancer.net/?p=2-88) there is a post," Learning from the Regrets of the Dying," listing some of the regrets other men shared about how they lived their life:

1. I wish I'd had the courage to live a life true to myself, not the life others expected of me.

2. I wish I didn't work so hard.

3. I wish I'd had the courage to express my feelings.

4. I wish I had stayed in touch with my friends.

5. I wish that I had let myself be happier.

We all can learn from the errors that others have made, there is no reason any of us need to repeat these errors.

The Treatment Process

Salvage Therapy- Your first attempt at treatment upon learning that you have had a reoccurrence should be salvage therapy, if you qualify. The hope is that salvage therapy will still provide a cure for your cancer. Salvage therapy **MUST** begin promptly, as soon as you know that your cancer has reoccurred. The appropriate salvage therapy will be dependent upon what was your primary treatment.

If The Primary Therapy That Failed Was	Your Possible Salvage Therapy Can Be
Radiation	Surgery; HIFU or Cryosurgery
Surgery	Radiation
HIFU	HIFU, Surgery or Radiation
Cryosurgery	Radiation or HIFU

In most of these salvage therapy attempts you should consider adding hormone therapy (ADT). There is a lot of research, especially in the situation of failed primary surgery, suggesting that a course of ADT does extend life.

Hormone Therapy (Androgen Deprivation Therapy -ADT) – If you try one of the salvage therapies and it fails, if you are initially diagnosed with recurrent prostate with a PSA above 10.0, or if there is evidence that the cancer has already moved beyond the gland (evidenced by positive scans or a bio-chemical reoccurrence with a PSA greater than 10) your best next treatment is hormone therapy (ADT).

ADT is a systemic treatment designed to treat the entire body as opposed to just a local spot. Some people mistakenly think that hormone therapy involves taking a hormone; on the contrary, ADT involves stopping the production of hormones (androgens) and blocking the body from using any androgens produced.

It has been shown that prostate cancer utilizes testosterone (the male androgen produced by the testes) to grow the cancer; some people liken testosterone as food for the cancer. It has been found that limiting the production of testosterone and blocking its ability to interact with the cancer cells tamps down the cancer and controls its growth by a process called apoptosis.

Prostate cancer that responds to hormone therapy is said to be hormone dependent. Unfortunately, in most cases, there comes a time that the cancer no longer responds to this therapy. At this juncture we refer to the cancer as being hormone resistant or castrate resistant prostate cancer (CRPC

What is Testosterone & How Can You Control It?

Testosterone, the male androgen which is most responsible for the initial growth of prostate cancer cells, is produced in the male testes. The testes produce the testosterone when they receive a signal, by way of a hormone called leuteinising hormone (LH) from the pituitary gland which is located in the brain. In turn, LH production is controlled by another hormone, leuteinising hormone releasing hormone (LHRH) which is produced in the hypothalamus. Ultimately the interaction of the pituitary, hypothalamus and the testes via the LH and the LHRH hormones is what regulates the production of testosterone. Whether via drugs or surgery, altering this inter-relationship among the three glands will modify the production of testosterone.

The goal of ADT is to lower your testosterone levels to less than 20 ng/ml. Some doctors feel that less than 50 ng/ml is adequate, but Malecare disagrees. When you have brought down your testosterone level to below 20 ng/ml you are castrate which is the goal for successful ADT.

There are different methods to obtaining a castrate level of testosterone. They are:

1- Surgically Controlling the Production of Testosterone

The production of testosterone can be controlled by a surgical procedure known as an orchiectomy. Orchiectomy consists of the removal of the gonads and the spermatic cord through an incision in the abdomen.

2- GnRH Agonists- Chemically Controlling the Production of Testosterone

In the alternative, the production of testosterone can be controlled by a class of drugs known as gonadatropin- releasing hormone (GnRH) agonists. These drugs are:

Zoladex

Lupron

Eligard

Viadur

Trelstar

Vantas

Synarel

These drugs have the ability to slow down the production of testosterone, thus depriving the cancer cells of the "fuel" needed to grow.

Caution - Recent evidence has confirmed that these drugs do increase your risk for developing diabetes, and heart problems. As of November 2010, the FDA is requiring that there be "Black Box" warnings on these drugs because they have been linked to increased cardiovascular risks, i.e. myocardial infarctions and cardiac deaths. If you are already taking, or are considering starting any of these drugs, consider making an appointment with a cardiologist and make sure that your doctor regularly monitors your blood sugar and possible signs of any heart damage.

Because of the loss of testosterone, GnRH agonists and an orchiectomy often will cause you additional side effects. The amount, incidence and the level of these side effects varies widely among different men. Some men report that they "barely" experience any side effects while others a report very significant impact from the side effects. There is no way to predict how you will experience these potential side effects. The side effects can consist of, but might not limited to:

Increased risk of developing cardiovascular complications

Increased risk of developing diabetes

Increased risk of developing Colorectal Cancer (Journal of the National Cancer Institute, 2010)

Hot flashes

Loss of muscle mass

Loss of Libido

Shortness of breath

Increase of blood pressure

Confusion

Disorientation

Weight gain

Neuropathy

Breast Growth (gynomastia)

According to a 2010 report from the American Society of Clinical Oncology "endurance, upper extremity strength and the physical components of the QOL are affected within 3 months of starting GnRH agonists". Exercise programs should start with the beginning of therapy because they have been shown to reduce the deterioration associated with long term ADT.

CAUTION: At least ten (10) days prior to starting a GnRH agonist, take an antiandrogen (see below). When you first start the GnRH agonist your body will start a cycle and over produce testosterone. This flooding of testosterone will enhance and encourage the prostate cancer to grow in leaps and bounds. For men with very advanced disease this can result in a significant disease progression and increased pain. (When this happens there will be what is called a PSA flare, the PSA will shoot up marking the increased growth and progression of the disease).

3- GnRH Receptor Antagonist-Another Chemical Way to Control the Production of Testosterone

Degarelix, recently approved by the FDA for the treatment of advanced and recurrent prostate cancer, has an immediate onset of action, binding to gonadatropin-releasing hormone (GnRH) receptors in the pituitary gland. This induces a fast and profound reduction in testosterone without the need to use an anti-androgen (see: Anti- Androgens).

The most serious of the possible side effects are:

Difficulty breathing

Swelling of the face, lips, tongue or throat

Dizziness, fainting or pounding heartbeat

Pain or burning during urination

Swelling in your hands, ankles, or feet

Dangerously high blood pressure (severe headache, blurred vision, buzzing in your ears, anxiety, confusion, chest pain, shortness of breath, uneven heartbeats or seizures

If you experience any of these you should immediately go to a doctor or emergency room.

4- Anti-Androgens - Blocking Testosterone from Accessing the Cancer Cells

Many doctors will add another drug to hormone therapy that will block the androgen receptors from accessing any testosterone that might still be produced. These drugs are called antiandrogens. When used in combination with drugs that restrict the production of testosterone the treatment is called combined therapy. The commonly used antiandrogen drugs in use are:

Casodex (bicalutamide)

Eulexin (flutamide)

Nilutamide (Nilandron)

Androcur (cyprotertone acetate)

Antiandrogens also can have their own side effects, which will vary from man to man:

Affect the liver

Cause hot flashes

Cause breast tenderness or growth

Cause the loss of libido

An anti-androgen drug should be taken 10 days prior to starting a GnRH Agonists.

A Long Simmering Controversy – The Use of a 5-alpha-reductase

An enzyme, 5-alpha-reductase, is responsible for the conversion of testosterone to 5α-dihydrotestosterone (5α-DHT) which is three times as potent as testosterone for prostate cancer cells due to its greater affinity for androgen receptors.[(]Wright, A. S., L. N. Thomas, et al. (1996). "Relative potency of testosterone and dihydrotestosterone in preventing atrophy and apoptosis in the prostate of the castrated rat." J Clin Invest 98(11): 2558-63.)

Some clinicians recommend that their patients to use 5α-reductase inhibitors (5-ARIs) like finasteride ((Proscar, Propecia) or dutasteride (Avodart) believing that it would extend their off periods from hormone therapy if they were using intermittent hormone therapy (IHT). In reality there exists very little evidence that supports this recommendation.

Like any other drug the 5α-reductase inhibitors have side effects. Among the most common side effects are gynecomastia (breast enlargement) and the loss of ejaculate.

What is Osteoporosis and How Is It Related to Hormone Therapy?

As we age it is normal for us to develop osteoporosis, a general loss of bone mass that can lead to fractures. Usually, osteoporosis is thought of as a disease of older women; however, it is also common in men. Hormone therapy (ADT) significantly increases a man's risk of developing osteoporosis. The

longer we remain on ADT, the greater our risk for developing osteoporosis. (*MICHAEL G. OEFELEIN, VINCENT RICCHUITI, et.al., J of Urology; Volume 166, Issue 5, Pages 1724-1728 (November 2001)*

When you have developed osteoporosis you will not experience any symptoms until a fracture occurs. Fractures of the spine are very common and may be caused by simple motions, by bending, lifting, or other minimal stress. Pain comes from the collapse of the small bones of the spine that may be may be made worse by standing or sudden movements. Early diagnosis and treatment are the most effective ways to prevent these potentially disabling fractures.

How is Osteoporosis Diagnosed?

Early diagnosis of osteoporosis is important, especially for men on ADT. You can be tested for osteoporosis by having your bone mineral density (BMD) evaluated by a DXA (dual energy x-ray absorptiometry) scan. The scan is both safe and painless.

How Is Osteoporosis Treated and Prevented?

Osteoporosis can be prevented and treated using several different approaches:

1- Change unhealthy habits including smoking and excessive use of alcohol.

2- Although there is some disagreement, it may be helpful to take calcium and vitamin D3.

3- Exercise regularly.

4- Talk to your doctor about taking an oral (not IV) bisphosphonate. Denosumab, marketed as Xgeva™, just approved by the FDA for men on ADT, has been shown in clinical trials to increase bone density and prevent fractures in men who develop osteoporosis as a result of androgen deprivation therapy. Denosumab has been demonstrated to be more effective in reducing bone fractures than zoledronic acid, the prior standard of care.

Anti-Androgen ADT Monotherapy

Some doctors will initially use only an antiandrogen drug as a monotherapy. Anti-androgen drugs block testosterone from interacting with the androgen receptors on the prostate cancer cells. Side effects from antiandrogen monotherapy are not as significant as when ADT is coupled with a drug that will also limit the production of testosterone.

Although it is rare that a doctor in the United States will offer antiandrogen monotherapy, the 2007 guidelines from The American Society of Clinical Oncologists (ASCO) for initial ADT says, “nonsteroidal antiandrogen monotherapy merits discussion as an alternative to combined androgen blockage (CAB) (50 mg Casodex with a GnRH agonists).

Casodex (150mg/qd) monotherapy has become the established alternative treatment to GnRH agonists in Europe. In men with biochemical recurrences only, this dosage of Casodex provides comparable outcomes, while preserving bone mineral density, muscle strength as well as other quality of life advantages. In men with demonstrated metastases, monotherapy is not as effective as CAB.

Timing of Hormone Therapy – When to Start Therapy and How to Structure It

Historically, hormone therapy was not started until a man had bone metastases and was experiencing pain from these metastases. Further, it was not clear if one type of hormone therapy, combined or monotherapy was superior to another.

Data from the NCI Intergroup Trial randomized men with minimal metastatic disease to monotherapy or to a combined androgen blockade (CAB) using both a treatment to stop the production of testosterone and another to block the existing testosterone from acting with the androgen receptors on the cancer cells. Results show that survival time appears to be much greater with CAB for the men with metastatic disease. This observation and other studies confirming the benefits of the early utilization of hormone therapy, lead us to conclude that early treatment with CAB in men with metastatic disease will improve survival time compared to waiting until symptomatic metastasis occurs. In fact, there is now a trend in the oncologic and urologic communities to treat men earlier with CAB, before symptoms develop.

Timing of Hormone Therapy- Intermittent (IHT) vs. Continuous Therapy

Traditionally, ADT was administered on a continuous basis, once on ADT a man stayed on it for the remainder of his life. Over time, it has become very clear that ADT itself poses significant risks to a man's life as well as to his quality of life (QOL).

Some doctors have started to experiment by changing the scheduling of the administration of ADT. Instead of keeping a man on therapy continually, they start and stop therapy by monitoring their PSA levels. Most of us survivors refer to the off therapy period as being on vacation (I will let you figure out why it is so named).

From the Advanced Prostate Cancer Blog:

"A Report From The Impact Conference On Intermittent Androgen Blockade" http://advancedprostatecancer.net/?p=155 –reported that an intermittent androgen blockade appears to delay the progression from treatable androgen-dependent cancer to untreatable androgen-independent disease (castrate resistant prostate cancer).

"Continious ADT vs Intermittent – There is a Winner From This Trial" http://advancedprostatecancer.net/?p=539 reported that side-effects were more pronounced in the continuous arm. Men treated with intermittent therapy reported better sexual function. The conclusions of the researchers was that IHT should be considered for use in routine practice because it is associated with no reduction in survival, no clinically meaningful impairment in QOL, better sexual activity, and considerable economic benefit to the individual and the community.

"Comparing Intermittent To Continuous Androgen Deprivation For Advanced Prostate Cancer", http://advancedprostatecancer.net/?p=386 concluded that IAD appears feasible for patients with locally advanced, hormone sensitive prostate cancer.

"Intermittent Hormone Blockade is Safe & Effective"; http://advancedprostatecancer.net/?p=73 ; The study showed that IAS is safe. The men on IAS experienced a 40% "off time" while also experiencing an increase in a positive quality of life.

Managing the Side Effects of ADT

As we have discussed, the potential side effects of ADT can be both bothersome and serious. It is imperative that you work closely with your doctor on developing strategies to improve the quality of your life (QOL) and keep you out of harms way. The advanced prostate cancer blog has a number of posts specific to managing these side effects.

"How to Manage the Side Effects of Hormone Therapy (ADT) in the Treatment of Prostate Cancer" http://advancedprostatecancer.net/?p=803.

"Long-Term Effects of Intermittent Androgen Suppression on Testosterone Recovery and Bone Mineral Density: Results of a 33-Month Observational Study", http://advancedprostatecancer.net/?p=547 reported that the bone mineral density partially recovered in men who recovered their testosterone levels during a vacation or "off period. "

Breast Enlargement- Gynecomastia- What Is It & How Can I Cope With It?

Gynecomastia, breast enlargement, is a common side effect from many prostate cancer treatments, specifically hormone therapy (ADT) and 5-alpha-reductase inhibitors. For many men, gynecomastia is a taboo subject. Men have a hard enough time talking about prostate cancer, but discussing breast growth can be overwhelming. Gynecomastia can be uncomfortable, even painful and for many of us it is embarrassing.

Some men have enlarged breasts simply because they are overweight. Gynecomastia is not extra fat tissue, but it is an enlargement caused by the breast's glandular tissue. This glandular tissue is located under the nipple and is not spread around the entire breast as is fat tissue.

There are a number of potential treatments available for men with gynecomastia. Radiation, surgery and taking tamoxifen (an anti-estrogen drug used in the treatment of breast cancer) all can have the effect of reducing gynecomastia. However, Malecare urges you to consider passing on all the treatments if you can cope with having gynecomastia. All these treatments are invasive and could cause a host of other negative side effects. Remember, gynecomastia is only cosmetic. Don't worry; gynecomastia does not change your risk for developing breast cancer. (http://advancedprostatecancer.net/?p=287)

Castrate Resistant Prostate Cancer (CRPC)-Formally Called Androgen Independent

In the normal course of prostate cancer progression the disease will stop responding to hormone therapy (ADT). It is not clear why this happens, but there are a number of theories.

1- Some doctors believe that there are cells that are able to survive with only very low levels of testosterone. Eventually, these cells which are able to survive during ADT proliferate and become the more common cancer cells.

2- Some doctors believe that during the course of ADT some of the cancer cells mutate and gain the ability to grow despite the low levels of testosterone

3- Some doctors believe that the androgen receptors mutate and are able to take better advantage of the low levels of testosterone

4- Some doctors believe that other organs, maybe even the cancer cells themselves, find a way to make their own, low levels of testosterone

No matter what the actual reason or reasons, developing castrate resistant prostate cancer is a significant step in the progression of your disease.

At this juncture, despite your being on ADT, your PSA will again climb, signaling that the cancer has again begun to progress. When facing this moment your first response should be to confirm that you have actually achieved a castrate level (less than 20 ng/ml) of testosterone production. Testosterone levels should be monitored on a regular basis while you are on ADT. If you are at a castrate level and your PSA is climbing, you have developed castrate resistant prostate cancer (CRPC).

When facing CRPC some doctors will recommend that you move on to chemotherapy using docetaxel (Taxotere). However, many of us believe that the use of chemotherapy should be further delayed by using a Second Line Hormone Therapy instead of chemotherapy.

Second-Line Hormone Therapy

The second-line hormone therapies that are commonly used are not approved for advanced prostate cancer, but there is still good evidence that they can control PSA and perhaps extend life. Each of the second-line therapies has its own unique potential side effects.

1- Anti-androgen withdrawal (AAW) is an excellent option for men who have been taking an anti-androgen drug including: Casodex, Eulexin , Nilutamide or Androcur. These drugs, which initially block the cancer cell from using the androgens, can begin to support the cancer, so stopping them can suppress the cancer and its growth. There are no side effects associated with AAW, but its response is often short lived.

2- On the opposite side of the coin, for those men who have not taken antiandrogen drugs adding them to the protocol can suppress the cancer by virtue of their ability to block the cancer from utilizing the androgens. Possible side effects include liver damage, hot flashes, breast growth and tenderness, loss of ejaculate, on rare occasions breast cysts and the loss of libido.

3- Estrogens can also control testosterone levels in the blood and they might also directly kill tumor cells. Estrogen therapy can cause blood clots; they increase the risk for cardiac events and can cause breast growth and pain. Estrogen therapy can be administered by injection, IV, pills, gels or patches. The optimum method is by patches because it allows better dosing control and and avoids any stomach complications.

   Caution - We recommend that men who have a family history of breast cancer have genetic screening and testing for the BRCA mutation prior to taking any estrogen treatment.

4- Ketoconazole (Nizoral) (Keto) which is an antifungal drug has been shown to be effective by temporarily decreasing levels of testosterone. Normally given in higher doses (800-1200mg/day) it can produce an effective, but temporary, hormone blockade. Since it has a different action, it blocks the androgens being generated in the adrenal gland, it can prove itself even after the LHRH drugs fail to provide an effect. Keto can cause nausea, vomiting and abdominal pain. If high doses cause you too much QOL issues it is possible to take it at lower doses and still receive a benefit. Keto must be taken with an acid stomach (drink orange juice along with the pill) and it must be taken religiously every eight hours without fail. Do not drink grapefruit juice with keto as it nullifies much of its action.

What Are Bone Metastases?

Bone metastases are tumors that have spread from the original cancer site in the prostate gland to your bones. The most common sites for them to develop are in your pelvis, spine, thighs and ribs, but they can develop in any bone anywhere in your body.

Normal bone is constantly being remodeled, or reabsorbed and then reformed. Prostate cancer disrupts the balance between the osteoclast cells that break down or reabsorb the old bone and the osteoblast cells that create new bone. When the balance is disrupted, tumors develop that can cause fractures, spinal compression, severe pain, weakness, numbness and trouble urinating. Bone metastases can also cause hypercalcemia (abnormally high levels of calcium in the blood causing constipation; nausea; pain; poor appetite; vomiting; kidney problems with flank pain; frequent thirst; frequent urination and kidney stones).

Detecting Bone Metastases

Since bone metastases symptoms can vary from man to man it is important to be able to correctly diagnosis bone metastases from other problems, like arthritis. If you experience bone pain it is important to tell your doctor. Bone metastases can be best diagnosed by x-rays, bone scans, CT scans, PET scans, MRIs and blood tests.

If bone metastases go without treatment, on the average, a man with castrate resistant prostate cancer will experience approximately 1.5 skeletal related events (SREs) annually (Saad F, Gleason DM, Murray R, et.al., J Natl Cancer Inst. 2002;94;1451468) with a median time to the first SRE of 10.6 months (Saad F, Gleason DM, Murray R, et.al., J Natl Cancer Inst. 2002;94:1458-1469). Bone Metastases need to be treated not only because they can cause severe pain, but they also cause bones to weaken and break. Uncontrolled progression of bones mets can completely disable a man. Bone metastases can cause spinal cord compression which can be fatal.

Preventing and Treating Bone Metastases

There are a number of different treatments that will affect bone metastases including chemotherapy, hormonal therapy (ADT), radiation therapy and bisphosponates. All of these therapies can affect the progression and growth of bone metastases.

Specifically, radiation therapy and bisphosphonates are designed to target bone metastases.

1- External Beam Radiation Therapy (EBRT) can be aimed at sites of painful bone metastases. EBRT relieves pain in the majority of men and is most useful for treatment when there are only one or two sites of pain. When there are more than one or two sites a systemic treatment, one that circulates through your body, is better.

2- Radiopharmaceuticals, a systemic treatment, are drugs given by intravenous infusion (IV). Commonly used radiopharmaceuticals are strontium-89 (Metastron®) and samarium-153

(Quadramet®). Two other radioactive isotopes, rhenium 86 and rhenium 188 are less commonly used to treat bone metastasis from prostate cancer.

These drugs usually are successful in relieving pain from bone metastases. They travel throughout the skeleton and are able to directly target the metastases in the bone so they are most effective for men with a number of different and diffuse painful bone metastases.

Strontium chloride (strontium-89) is the most common radiopharmaceutical for treating men with prostate cancer that has metastasized to the bone. Men with advanced prostate cancer who are responding to chemotherapy appear to have a better chance of survival if bone metastases are treated with strontium-89 every six weeks in conjunction with a chemotherapy drug.

Dosages of radiopharmaceuticals vary with the individual and the type of treatment. Dosages of radioactive materials are expressed in units called millicuries.

Strontium-89 is injected into a vein. The usual dosage is 4 millicuries, depending on age, body size, and blood cell counts. Repeated doses may be required.

The usual dosage of samarium 153 is 1 millicurie per kg (0.45 millicurie per lb) of body weight, injected slowly into a vein. Repeated doses may be necessary. Because samarium 153 may accumulate in the bladder, it is important to drink plenty of liquid prior to treatment and to urinate often after treatment.

Strontium-89 and samarium 153 may temporarily lower the number of white blood cells, which you need to fight infections. The number of blood platelets which are important for proper blood clotting may also be lowered. You can take some precautions for reducing your risk of infection and bleeding:

Avoid people with infections

Seek medical help at the first sign of infection or unusual bleeding

Use care when cleaning your teeth

Avoid touching the eyes or the inside of your nose

Avoid cutting or injuring yourself

Strontium-89 and samarium 153 are excreted in the urine. To prevent radioactive contamination, you should follow special measures for one week after receiving strontium-89 and for 12 hours after receiving samarium 153:

Use a toilet rather than a urinal

Flush the toilet several times after each use

Wipe up and flush any spilled urine or blood

Wash your hands after using or cleaning a toilet

Wash soiled clothes and bed linens separately from other laundry

If you suffer with bladder control problems you must take special measures following treatment to prevent contamination with radioactive urine. Speak to your doctor about this prior to treatment.

Flushing and transient increased bone pain are among the more common side effects of strontium-89.

Less common side effects of samarium 153 include:

- irregular heartbeat
- temporary increase in bone pain
- nausea and vomiting

Signs of infection due to low white blood cell counts after treatment with strontium-89 and samarium 153 are fever or chills, cough or hoarseness, lower back or side pain, painful or difficult urination

Signs of low platelet count after treatment with strontium-89 and samarium 153 include, bleeding or bruising, black, tar-like stools, blood in urine or stools and tiny red spots on the skin

Radiation therapy or anticancer drugs may increase the harmful effects of strontium-89 and samarium 153 on the bone marrow. Medicines containing calcium may prevent strontium-89 from being taken up by bone tissue. Bisphosphonates may prevent samarium153 from working effectively.

3- Bisphosphonates are a class of drugs that keep bone from breaking down or becoming reabsorbed. Zoledronic acid (Zometa®) is the most commonly used bisphosphonate in men with advanced prostate cancer. Zometa not only reduces the risk of developing bone complications, it also treats existing bone metastases. Zometa is prescribed for men with castrate resistant prostate cancer after the failure of one hormone type of treatment (not to be confused with taking oral bisphosphonates to maintain bone mineral density (BMD).

   Before starting on any IV bisphosphonate, in order to avoid developing Osteonecrosis of the Jaw (ONJ- a disfiguring and disabling condition where the jaw bones suffer literal bone death through infection and rotting) you should have a comprehensive dental examination and complete all dental work that you need. While receiving treatment it is vital that you maintain excellent oral hygiene. Try to avoid all invasive dental procedures and make sure that your dental professionals know that you are receiving IV bisphosphonates.

   Zometa is administered by infusion (IV). It is very important that you are very well hydrated (drink a lot of water prior to the infusion and during it) and make sure that during the treatment your electrolytes are monitored by the infusion staff. A small number of men experience incapacitating bone, joint and/or muscle pain. If you do, discontinue the bisphosphonate treatment. In order to minimize side effects, we recommend that you ask your doctor to time your initial infusion rate to not less than one hour and then not less than 30 minutes for each subsequent infusion.

4- Since bone metastases can be painful, the use of pain medications is an important part of care for most men. If you are in pain let your doctor know and ask for pain medication as needed. There is never any good reason that you should not take adequate pain medication so that you are comfortable.

5- In situations where you experience a fracture or a spinal compression surgery is commonly used to repair any damage to your bone. Spinal compression is very serious as it can cause paralysis, so it must be quickly treated.

Lymph Node Metastasis

Our bodies normally produce fluid called lymph which circulates through the lymphatic system. The lymph fluid is made up of white blood cells that are filtered by small oval or circular organs called lymph nodes. Cancerous cells that circulate through the body can become trapped in the lymph nodes and will sometimes develop metastases in the lymph nodes themselves.

Other Soft Tissue Metastasis

Metastases are not always limited to either bone or the lymph nodes. Any soft tissue organ can develop prostate cancer metastases. If you develop a tumor in another organ it is very important to have your doctors determine if the tumor is a spread of the prostate cancer or is another unrelated cancer.

Chemotherapy

Chemotherapy is the treatment of a disease, including cancer, with any type of chemical. It would be technically accurate to say that any prostate cancer treatment using a drug of any type is chemotherapy. However, common usage of the word chemotherapy in the treatment of prostate cancer is usually reserved for treatments using the drugs docetaxel (Taxotere) and cabaziltaxel (Jevtana).

Taxotere

The US Food and Drug Administration (FDA) approved Taxotere (docetaxel) in May 2004 for men with castrate resistant, metastatic disease. Taxotere is administered by intravenous infusion (IV) in combination with the steroid prednisone. Taxotere, along with prednisone infusion is given every three weeks; however current practice is that men who have too much difficulty with side effects will have a reduced Taxotere dosage administered every week.

Taxotere showed itself to be safe and effective in the TAX327 clinical trial of over 1,000 men. Taxotere was compared to the then standard of care for men with castrate resistant prostate cancer who had bone metastases. In this trial Taxotere provided a survival advantage of 2.5 months over the control group being given the then standard of care, mitoxantrone.

Taxotere chemotherapy is systemic, so it works throughout your entire body. It works by targeting and killing rapidly dividing cells. Since cancer cells divide more quickly than healthy cells, more cancer cells are killed by the drug than are healthy cells. Taxotere will also kill healthy cells including the normally more rapidly dividing skin, hair follicle, gastrointestinal tract, and bone marrow cells.

The side effects that are commonly reported are nausea, hair loss (alopecia), and bone marrow suppression (low blood counts). Less common side effects include fluid retention and peripheral neuropathy (tingling feelings in the hands and feet).

Many men will require supportive care while taking taxotere.

As with all cancer therapies some men will respond while others will not. Most men have a positive response to Taxotere including a lowering of PSA, pain relief and changes in tumors as evidenced on scans. The length of response also varies with some men only experiencing the benefits for a few months while others have an extended benefit time.

There are some on-going clinical trials investigating whether giving Taxotere earlier will it provide additional efficacy. Anyone taking Taxotere who is not castrate resistant should be aware that they are actually on an experimental protocol.

For information on how to manage the side effects of Taxotere go to:
http://advancedprostatecancer.net/?p=1915

http://advancedprostatecancer.net/?p=1918

http://advancedprostatecancer.net/?p=1920

Cabazitaxel

Cabazitaxel (*Jevtana*) was approved by the FDA in June 2010 as a second-line chemotherapy to be used in advanced hormone refractory prostate cancer in men who have already been treated with docetaxel and then failed.

Cabazitaxel is the first chemotherapy to have shown any survival benefit for men with advanced castrate resistant prostate cancer since the approval of docetaxel.

The approval was based on data from the single company-sponsored phase III TROPIC clinical trial, conducted in 755 men. All the men who participated in the trial had advanced castrate resistant prostate cancer and all had previously been treated with and failed docetaxel treatment. They were randomized to receive either cabazitaxel or mitoxantrone, both in combination with prednisone.

In this setting the cabazitaxel demonstrated a median survival advantage of 2.4 months.

Cabazitaxel is a drug with many significant side effects. The most common adverse reactions (grades 1 to 4), seen in 10% or more of the men in the trial, were neutropenia (recurrent periods of a very low white blood cell count) , anemia (low red blood cell count), leucopenia (low white blood cell count), thrombocytopenia (low levels of blood platelets that cause clotting), diarrhea, fatigue, nausea, vomiting, constipation, asthenia (lack of muscle strength, malaise, dizziness and fatigue), abdominal pain, hematuria (presence of red blood cells in the urine) , back pain, anorexia (loss of appetite), peripheral neuropathy (pain, numbness and tingling in your arms, hands and feet), pyrexia (fever), dyspnea (shortness of breath), dysguesia (distortion of the sense of taste), cough, arthralgia (joint pain), and alopecia (hair loss). The most common adverse events leading to discontinuation of the drug were neutropenia and renal failure.

Warning - There are also warnings that the drug has caused neutropenic deaths (as with most chemotherapy drugs, Cabazitaxel kills many white blood cells that then leave a patient significantly more susceptible to life-threatening infections). It is very important that you aggressively monitor your blood count to avoid any dangerous occurrence of neutropenia.

Mitoxantrone

The combination of mitoxantrone and prednisone is FDA approved as a second-line treatment for metastatic castrate resistant prostate cancer. Until docetaxel (Taxotere) was approved for prostate cancer it was the standard of care. Since docetaxel demonstrated that it provided a survival advantage while mitoxantrone did not, Taxotere became the new standard of care. However, mitoxantrone does provide palliative benefits, so it remains in the arsenal of treatments for men with castrate resistant prostate cancer after both Taxotere and now cabazitaxel have failed.
(http://advancedprostatecancer.net/?p=626)

Possible side effects from mitoxantrone include:

1- Low blood counts which, can put you at risk for infection, anemia and bleeding.
2- Nausea and vomiting
3- Fever
4- Increases in problems with liver functions
5- Weakness
6- Mouth sores
7- Hair loss
8- Diarrhea
9- Heart problems (arrhythmia)
10- Low blood pressure
11- Blue/green discoloration of the eyes or urine.

Mitoxantrone can also have some delayed side effects:

Warning - A serious but uncommon side effect of mitoxantrone can be interference with the pumping action of the heart. You can receive only up to a certain amount of mitoxantrone during your lifetime. This "lifetime maximum dose" may be lower if you have heart disease risk factors such as radiation to the chest, advancing age, and use of other heart-toxic drugs. Your doctor may check your heart function before you may take any mitoxantrone and will monitor your heart periodically during your treatment.

There is also a slight risk of developing a blood cancer such as leukemia years after taking mitoxantrone, but to be honest at this stage this need not be a concern for men with prostate cancer.

Immunotherapy- Treating Cancer by Enhancing Your Own Immune System

Your immune system is designed to be able to identify foreign organisms that invade your body and then eliminate them. Cancer is the out of control growth of your own cells, so your immune system does not recognize cancer as a foreign organism. When you do develop cancer your immune system fails to recognize these abnormal cells as foreign objects, so it does not fight their continued development.

There has been a lot of effort in the past to devise ways to have the immune system respond to cancer, in most cases with very limited or no success. In May 2010, the FDA approved Sipuleucel-T (Provenge®), the first immunotherapy approved for any cancer.

In addition to Provenge, there have been significant developments of new candidate vaccines and therapeutic antibodies designed to target prostate cancer. There are currently 30 different candidates in the pipeline, 16 prostate cancer vaccines and 14 prostate cancer-targeting antibodies. Of these candidates, 19 are at Phases II and III (9 vaccines and 10 antibodies) and 8 are at Phase I trials.

These investigational vaccines and antibodies are targeting more than 15 different prostate cancer-associated antigens or other prostate cancer-associated proteins. There are 25 companies: 20 small and medium sized enterprises and 5 multinational pharmaceutical companies currently involved in this research.

The potential is clear; we are in an excellent position to see new immunotherapy in the not too distant future.

Sipuleucel-T (Provenge®)

Provenge, the first FDA approved immunotherapy for cancer, is considered a vaccine, but it differs from traditional vaccines as it is given after a disease is diagnosed. We think of vaccines as a defensive treatment, to prevent our developing an ailment; Provenge is administered after prostate cancer has developed. Provenge is a personalized treatment that teaches your immune system to recognize your prostate cancer as a foreign body and then fight it.

The approval of Provenge is very specific and is limited to men who have prostate cancer, who are castrate resistant, have metastatic disease and who experience minimal or no symptoms (pain).

Provenge is administered in a unique way. Dendritic cells, a type of white blood cell, are removed from you by a process called leukapheresis. Leukapheresis involves having your blood drawn from one arm by a catheter that is placed in one of your veins, a system that is used when you donate blood. A special machine extracts the dendritic cells from your blood and returns the rest of your blood product to you.

The removed dendritic cells are then shipped to a manufacturing plant where a prostate cancer antigen and some immune stimulating molecules are attached to the surface of your dendritic cells. These “supercharged” dendritic cells are then shipped back to the leukapheresis center to be returned to you by an infusion.

Provenge has little effect on PSA or tumor shrinkage. Despite this, Provenge demonstrated an increased survival time of 4 months (IMPACT TRIAL).

The most common side effects reported with Provenge are chills, fatigue, fever, back pain, nausea, joint ache, and headache. Side effects usually develop within a day or two of the infusion and last for only a day or two.

When to Use A Treatment & What Drugs Should Be Combined?

This recent approval of three new drugs for the treatment of prostate cancer (denosumb, Provenge and cabazitaxel) brings us to an important question about the proper timing of treatments as well as the efficacy of combing treatments to maximize survival. Looking into the near future, we will hopefully be adding a number of additional treatments to our approved list, so this question will become both more complex and more important.

For example, a small phase I trial combined docetaxel (Taxotere) and prednisone with different doses of Ketoconazole (Keto). The trial enrolled 42 men who had metastatic, castrate resistant prostate cancer (mCRPC). They were treated weekly with docetaxel and prednisone (D+P) every 3 of every 4 weeks plus a daily dose of Keto.

The researchers studied a variety of different doses of Keto and D+P. They found that by combining the therapies, PSA levels were lowered by 50 percent in 62% of the men and that 28% of the men who had soft tissue metastases had a partial response to therapy.

They also found that the median overall survival of the men was 22.8 months but by changing the timing of the treatments they found that there was a significantly greater survival in men who were D+P naïve than in men who had already been treated with D+P (36.8 vs 10.3 months).

The researchers also found that there was a correlation between D+P clearance (the time it takes for your body to rid itself of the drugs) and Keto. Keto increased docetaxel exposure 2.6-fold at a keto dose of 1,200 mg daily, 1.6-fold with 800 mg daily, and 1.3- to 1.5-fold with 600 mg daily.

The trial concluded that combination regimens using 600 mg keto daily were well tolerated and that the maximum tolerated dose of D+P in combination with keto was 32 mg/m2. They go on to suggest that this combination has significant anti-tumor activity in men with castrate resistant prostate cancer. *(J Urol. 2010 Jun;183(6):2219-26; A phase I clinical study of high dose ketoconazole plus weekly docetaxel for metastatic castration resistant prostate cancer.; Figg WD, Woo S, Zhu W, Chen X, Ajiboye AS, Steinberg SM, Price DK, Wright JJ, Parnes HL, Arlen PM, Gulley JL, Dahut WL. -PMID: 20399458)*

Dendreon, the company that manufactures Provenge, has recognized this question and is now running new clinical trials that are designed to evaluate the use of Provenge at different times in prostate cancer disease progression.

These studies raise the serious question about how we combine treatments and how we time treatments in the disease process. How we properly order and combine treatments to maximize our survival remains a great, important and yet unanswered question.
(http://advancedprostatecancer.net/?p=1677)

On the Horizon

There have now been three new prostate cancer drugs approved in the last year. Not since Taxotere's approval six years ago have we had any new prostate cancer drugs approvals. The really great news is that there are many other potential new drugs in the pipeline, or On The Horizon.

1- Abiraterone- (http://advancedprostatecancer.net/?p=1953 & http://advancedprostatecancer.net/?p=1249) Abiraterone is probably the most promising new potential drug on the horizon. We are anticipating a quick FDA approval as well as the possibility of an approval for compassionate use in the matter of a month or so (this is being written in the beginning of December 2010). Abiraterone is taken in combination with prednisone. It blocks the production of testosterone by inhibiting CYP17A1, an enzyme also known as 17α-hydroxylase/17,20 lyase. This enzyme is involved in the formation of DHEA and androstenedione which may ultimately be metabolized into testosterone. Abiraterone, in a phase III trial, extended survival by an average of 3.9 months among men with castration-resistant metastatic prostate cancer for whom other treatments, including chemotherapy with docetaxel, have failed.

2- MDV3100- (http://advancedprostatecancer.net/?s=mdv3100 & (http://advancedprostatecancer.net/?p=1458) MDV3100 is an exciting potential new "super" androgen blocker (anti-androgen). Currently, the most common anti-androgen we use is Casodex, but its useful life is very limited and it is not as effective a testosterone blocker as we need. We are in need of a more complete inhibitor of the Androgen Receptor (AR) and MDV3100 shows an indication of its potential to meet this need. In addition to their current Phase III trial, Medivation has announced their intention to start several additional trials to evaluate what is the best stage of prostate cancer to use MDV3100.

3- LX184- (http://advancedprostatecancer.net/?p=2162) LX184 is still very early in its testing, but has been characterized as being very intriguing. In very early testing 19 of 20 men in a phase I trial showed an improvement in scans. To the surprise of the investigators, in some of the men in the trial, the bone scans no longer detect any cancer despite prior confirming scans. Additionally, some of the men were able to stop taking the narcotics they were using to control their bone pain caused by the bone metastases.

4- PROSTVAC™- (http://advancedprostatecancer.net/?p=1529) Malecare is hopeful that the next prostate cancer vaccine to become available will be Prostvac. A successful phase II trial of 125 men with metastatic prostate cancer demonstrated a survival advantage of 8.5 months. Provenge's survival advantage based on their phase III data was a little over four months. According to the developing company, Bavarian Nordic, Prostvac, a therapeutic cancer vaccine, has received fast track status from the FDA. Additionally, the company has received Scientific Advice from the European Medicines Agency and has successfully concluded the required "end of Phase II meeting" with the US Food and Drug Administration (FDA). Both European Medicines

Agency and the FDA have indicated a preliminary agreement to conduct a phase III clinical trial. Like the Provenge trial, the study will be placebo-controlled using men with minimally symptomatic, castration-resistant metastatic prostate cancer after failure of surgery or radiotherapy.

One major difference between Provenge and Prostvac is the treatment protocol. Provenge is a personalized treatment that requires that a man's white blood cells first be removed and be shipped to a manufacturing plant where the cells are treated. After treatment the processed cells are infused back into the man. Prostvac is an "off the shelf" product that is administered subcutaneously to induce a specific, targeted immune response that attacks prostate cancer cells. Like Provenge, the morbidity issues seem to be mild.

5- TAK700- TAK700 (http://advancedprostatecancer.net/?p=2121) is a selective, oral, non-steroidal androgen synthesis inhibitor that in preclinical studies has been shown to selectively bind to and inhibit the enzyme 17,20 lyase in both the testes and adrenal glands. As a result TAK700 is believed to substantially reduce adrenal androgen levels in vivo.

A new randomized, double-blind, multi-center, global Phase III study will evaluate TAK-700 with prednisone compared to placebo with prednisone in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). Its primary endpoints are Overall Survival (OS) and Progression Free Survival (PFS).

A second new study will compare TAK-700 plus prednisone versus placebo plus prednisone in patients with mCRPC that have progressed during or following docetaxel-based therapy.

6- Custirsen – (http://advancedprostatecancer.net/?p=1990) According Results from a recent trial of investigational agent OGX-011/TV1011 (custirsen) in men with advanced prostate cancer showed a survival benefit when the men were treated with custirsen plus first-line docetaxel plus prednisone. The trial show almost a seven month survival increase when the men were treated with the standard of care, docetaxel plus prednisone. In addition, custirsen in combination with docetaxel was well tolerated by the men. (*Randomized Phase 2 Study of Docetaxel and Prednisone With or Without OGX-011 in Patients With Metastatic Castration-Resistant Prostate Cancer. Chi K.N., et al. JCO Sep 20, 2010: 4247-4254)*

7- Cyclophosphamide (Cytoxan®) (CP) (http://advancedprostatecancer.net/?p=1620) is another possible 2nd line future chemotherapy for castrate resistant prostate cancer after the failure of taxotere.

Low-dose CP (50 mg/d) and dexamethasone (1 mg/d) were given in a metronomic manner (repetitive, low doses designed to minimize toxicity and target the endothelium or tumor stroma as opposed to targeting the tumor) to 17 men. Treatment was continued until disease progression or intolerable side effects occurred.

Nine (9) men had a PSA response (median 44.4%); four men had a greater than 50% response and five men had a less than 50% PSA response. Eight men eventually experienced a PSA progression. The overall survival was 24 months. Five men reported a decrease in bone pain after 4 weeks of treatment. As opposed to Jevtana (cabazitaxel) the men did not report any grade 3 and 4 toxicities.

Further advantages of low-dose CP were its convenient oral administration, dosing schedule, low cost, and low-toxicity profile. These attributes in combination with immuno-regulatory and antiangiogenic potentials make Cyclophosphamideals a prime candidate for additional study for post chemotherapy and as a possible combination drug to be used with other treatment regimens. (*Med Oncol. 2010 Jun;27(2):569.; , Nelius T, Klatte T, de Riese W, Haynes A, Filleur S. PMID: 19365737 [PubMed - in process])*

8- Alpharadin (radium-223)- (http://advancedprostatecancer.net/?p=1611) is a new radiopharmaceutical (a drug that targets radiation to bone metastases) in development for the treatment of men with bone metastases.

9- Sodium Clodronat, (http://advancedprostatecancer.net/?p=2033#more-2033) a potential bisphosphonate drug has shown itself to increase survival. mproves Survival In Patients With Advanced Prostate Cancer But Not With Localized Disease

Clinical Trials

Clinical trials are the life blood of prostate cancer research and for the development of new, safer and more effective treatments. Trials not only advanced our knowledge, but they offer hope (look at all the new "On The Horizon" drugs we discussed in this booklet). Without trials we could not evaluate if a new treatment works or if it is just "snake oil" or if it is safe. Participating in a trial can benefit you now and it can benefit others in the future.

Clinical trials offer you hope, but they also offer some risk. When you are deciding if you are willing to participate in a trial you must learn about the possible benefits and the possible risks you might be subjected to in the trial.

What are the possible advantages of participating in a trial?

1- The experimental treatment or device might be effective and improve your situation.

2- You will contribute to our knowledge base about prostate cancer.

3- If the investigation drug or treatment works it might still be available to you after the close of the trial.

What are the disadvantages?

1- The drug or treatment might not help you.

2- You might be required to spend additional time at a doctor's office or the hospital.

3- You might experience side effects from the treatment.

4- Even if the treatment worked for you, if it is not also effective for enough other peple you might no longer be able to have the treatment.

5- You might not get the investigation drug, but instead be in the control group which gets only the standard of care treatment (you will never not receive care).

Before any drug or treatment reaches human trials there has been significant prior study of the investigation product. There have been pre-clinical trials (bench science) and animal studies. Even if you are in a phase I trial, the first human trial, the drug has already been well vetted.

Before deciding to participate in a trial you should speak with your doctor and the clinical trial coordinator and ask;

1- Is there strong evidence that this treatment will work for me?

2- Is it a randomized trial?

3- If it is randomized is there a chance I could get a placebo or are all groups going to receive the investigation treatment?

4- What are the risks and benefits that I might experience?

5- If I do well on the investigation treatment will I be able to continue to have it even after the trial has stopped?

6- What additional things will be required of me if I participate in the trial? Will there be additional tests or scans, doctor or hospital visits required? Make sure that you understand how much extra time and effort will be required from you.

7- What additional financial costs will I have to carry? Usually, the research costs will be paid for by the researchers, but you or your insurance company might remain responsible for your routine patient care costs. Make sure that your insurance company will pay for these costs while you are on an experimental therapy.

8- If you change your mind about participating, or you believe that the trial is not working for you always have the right to stop participating.

When Should I Participate In A Trial?

There are appropriate trials for prostate cancer at all stages of disease progression. Many of us look to trials only when we feel there are not any alternative treatments available to us. Trials are important at all stages and you should consider participating in a trial even if there are still treatment options open to you.

What Are The Different Trials?

Clinical trial research progresses in an orderly series of steps, called phases. The phasing of trials allows researchers to ask and answer questions in a way that results in reliable information about the investigation drug or treatment while also protecting the patient. Clinical trials are classified into one of three phases:

1- Phase I trials: These first studies in people evaluate how a new drug should be given (by mouth, injected into the blood, or injected into the muscle), how often, and what dose is safe. A phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen.

2- Phase II trials: A phase II trial continues to test the safety of the drug, and begins to evaluate how well the new drug works. Phase II studies usually focus on a particular type of cancer.

3- Phase III trials: These studies test a new drug, a new combination of drugs, or a new surgical procedure in comparison to the current standard. A participant will usually be assigned to the standard group or the new group at random (called randomization). Phase III trials often enroll large numbers of people and may be conducted at many doctors' offices, clinics, and cancer centers nationwide.

In addition, after a treatment has been approved and is being marketed, the drug's maker may study it further in a phase IV trial. The purpose of phase IV trials is to evaluate the side effects, risks, and benefits of a drug over a longer period of time and in a larger number of people than in phase III clinical trials. Thousands of people are involved in a phase IV trial. (from the NCI Web page: http://www.cancer.gov/clinicaltrials/education/what-is-a-clinical-trial)

You can read Malecare's frequently asked question guide about clinical trials at:

http://malecare.org/clinical-trials-faq/

We also recommend that you go to: **http://tinyurl.com/2cxtd8j** and register to receive clinical trial updates and announcements for trials that might interest you.

A Survival Advantage – Is It Worth It and What Does It Mean?

In order to get FDA approval, drugs must first go through a clinical trial that demonstrates that they offer a better treatment result than the current standard of care. In some instances, the better result

can be a demonstration that the investigational drug provides an advantage which is only palliative (as Mitoxantrone does for advanced prostate cancer), but the best treatment result is survival. Survival is the gold standard of positive results; extending life is the ultimate goal.

The pivotal clinical trial for prostate cancer chemotherapy using taxotere showed that it provide a median of 2.5 months additional survival over the then standard of care, Mitoxantrone. Cabazitaxel, which was just approved by the FDA to treat men who have failed chemotherapy with taxotere, provides a median of 2.4 month additional survival time and Provenge adds an additional median of 4.1 months of survival.

Recent debates about the value of these survival advantages have rocketed into the public consciousness as the median survival advantages for all these drugs have been measured only in months while all these treatments come with extra side effects and significant additional economic costs. The big question is are these extra months of survival really worth the possible negative effects on your quality of life and are they worth the economic burden they place on your family and on society in general?

Malecare's opinion is a very clear and very strong YES.

Why do I feel this way?

Survival advantages are expressed in statistics and statistics are just a way to express general group trends. Statistics do not imply any guarantee, or even useful information, at the individual, personal level. The simplest way I can explain this is by sharing what my statistics 101 teacher said on the first day of class, "Ten women are in a room and one is pregnant. He then stated that from a statistical point of view it is possible to state that each woman is 10% pregnant." We all know the absurdity of this statistically correct statement. Statistics are excellent in a large group trend analysis, but statistics are worthless when it comes to understanding the individual situation. Statistics do not provide any insight into what you can personally expect for yourself; they don't express your individual situation. A statistical analysis of a trial will not give you any insight into what your personal experience might be if you take a drug or treatment.

Statistics are constantly being interpreted, often leading to the detriment of understanding the potential upside of a drug or treatment for an individual. Survival statistics are expressed as a median and the median is the actual number that lies in the middle. A median is not an average, so don't get confused. If a trial evaluated survival time, one half of the people in a trial lived longer than the median and one half survived less than the median number. The median does not take into account how long the men on the right side of the curve, the side that expresses a longer survival advantage, lived. It is theoretically possible that all the men on the right side of the curve could have lived for 50 more years while all the men on the left side died the day after receiving the treatment. Survival statistics do not attempt to explain what actually happened to the individual person, neither to the person who was on the left side or the right side of the curve.

Any one of us, actually one half of us, will be on the right side of the curve and live longer while the other half will have died. By taking a treatment you have a 50% chance of being in the better responding group, you have the hope of being a person who lives much longer, maybe 50 years longer!

The way most clinical trials are conducted, the median number often becomes blurred and contaminated. The studies that were conducted for the drugs, taxotere, Provenge and Cabazitaxel all allowed men in the placebo group to cross over to the treatment arm once they showed signs of disease progression. This means that men in the placebo group, the group that did not receive the investigational drug, were allowed to receive the treatment, but their survival time was still calculated as if they never received the investigational treatment. Since receiving the treatment extends life, the survival statistics for the control placebo group might also have been extended beyond what they otherwise would have been.

Since the investigational drug did extend life, the fact that men in the placebo group were allowed to received the treatment probably added to their actual survival time, statistically shrinking the difference in the survival differences between the two groups. The bottom line is that the survival time of the placebo arm was probably inflated, reducing the survival advantage of the treatment arm.

So, are these treatments worth it? Our unabashed answer is yes, they certainly provide hope and they do provide life extension, possibly well beyond the statistical survival advantage we see from the clinical trials.

Conclusion

None of us would willingly choose to live with recurrent prostate cancer, but having this disease is not the end of the world, nor is it the end of your life. There are many ways to battle our disease while we continue to live a happy and healthy life.

To accomplish this we need to learn as much as possible about our disease, take responsibility for our own health and treatment decisions and find ways to enjoy ourselves.

Appendix

Thoughts –Taken from the Advanced Prostate Cancer Blog at: www.advancedprostatecancer.net

*

Happiness is taking pleasure in what you do have.

*

Everyday set aside some time to ask yourself two important questions;

1- What am I living for?

2- What can I do or change and to make the world a better place?

*

"Pain is part of being alive, and we need to learn that. Pain does not last forever, nor is it necessarily unbeatable, and we need to be taught that." – *Rabbi Harold Kushner, popular speaker and author of numerous books, including When Bad Things Happen to Good People*

*

The doctors told me that I have recurrent prostate cancer, they stamped on my forehead a little sign that says "EXPIRES ??/??/20??. I have tried and tried to wash that stamp off my face. No matter what I do it still remains, setting me apart from everyone else. I am not ready to expire nor am I " Best By ??/??/20??", the other stamp that has recently appeared.

*

Having cancer gives notice, notice that we will expire, but there are still remains question marks on the dates. We know these dates exist, that they are real. We know that they will rear their ugly heads sooner than we ever expect and sooner than we otherwise would wish. But, we do know they are there, serving as a warning to us and all the people who can read those stamps.

I am not feeling ready to die. I have things I want to experience, things I want to see, things I want to be a part of, but I also know that I have been given notice, I have been stamped, whether I like it or not.

So, I need to find a way to do as much as possible each and every day. I need to see everything around me and embrace it all. I need to extend that "SELL BY" date (I also have one of those) while also using every day before the expiration date as best as possible.

*

If I am not prepared, I have nobody but myself to blame. I am not into blaming myself for anything, so I will continue to use everyday left to the fullest I possibly can. **So should you.**

*

Some mornings when I first wake up I am more like a normal man. I don't remember that I have cancer, then the lightning bolt hits and I remember, I have cancer! I remember that I am going to die because of this and there is little that I can actually do to remedy the situation.

*

If I am able, after the realization hits, I try to sink back into my mattress, pull the covers over my head and will myself back to sleep. My goal is simple; I look for oblivion, where conscious thought doesn't exist.

*

More often than not, I can't fall back into sleep and my cancer reality stays front and center. Feeling overwhelmed, I decide to get going and live my life. I manage to get my sorry ass out of bed and I put on my armor to fight another day.

*

I have also learned that some things are just completely out of my control.

---

*

It must be borne in mind that the tragedy of life doesn't lie in not reaching your goal.

The tragedy lies in having no goal to reach.

It is not a calamity to die with dreams unfulfilled.

But it is a calamity not to dream.

It is not a disaster to be unable to capture your ideal,
But it is a disaster to have no ideal to capture.

It is not a disgrace not to reach the stars.

But it is a disgrace not to have stars to reach for.

Not failure, but low aim is a sin.

Dr Benjamin Elijah Mays
1894-1984

*

I cannot forget the many stories I hear about how people's positive attitude and positive thinking allows them to recover from situations that are hopeless. I believe if you expect to be sick you will be sick. If you expect to get well your chances of being well are much better, there is no guarantee, but why not shoot for the stars?

Outcome, at least with cancer treatment, **has a lot to do with expectations.** We have some control over whether we will become victims or victors. Think positive, accept everything but always stay positive.

*

Today the movie version of Maurice Sendak's 1963 children's picture book, "Where the Wild Things Are" opens in theaters.

When the book was first published, many people complained that it was too scary. Sendak's response was simple, he said just don't read it.

Sometimes, whether you read a book or watch a movie is not a choice you have. Sometimes, we cannot just walk away from our monsters by not seeing a movie, not reading a book or by not looking under our bed.

Sometimes we need to deal with our monsters. As Max did, we need to tame our monsters by staring directly into their yellow eyes and not flinching.

We too are capable of taming our monsters and becoming king of our own Wild Things.
