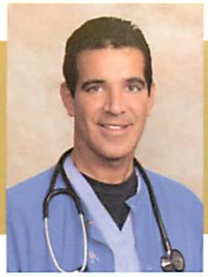


Recurrence: An Update

MESSAGE FROM MICHAEL DATTOLI, MD

Five years ago, we published an article in the Spring 2012 issue of *Journey* entitled "New Options in Metastatic Prostate Cancer Treatment." Provenge®, a form of immunotherapy, had just been FDA approved and was finding its way to patients who had exhausted hormone therapy and chemotherapy. While the reported overall survival improvement from using the drug was only four months, this positive direction gave new hope to many who were facing failure. Research developing Provenge also led to similar prostate immunotherapeutic agents, including Prostvac®, which hopefully will soon be approved by the FDA.

Also debuting around that time were Zytiga®, Xgeva® and Jevtana®, which are now among the agents regularly prescribed for recurrence of prostate cancer. Additionally, Xofigo® (radium -223), an alpha particle radioisotope, can be delivered in a one-minute infusion which attacks prostate cancer that has spread to bones. Xofigo not only relieves bone pain, but also improves overall survival. Xofigo is now being combined with Zytiga, Xtandi® and Provenge, and the combination appears to be synergistic.

Whereas Xofigo only treats bone, another injectable radioisotope called actinium-225 attaches to prostate-specific membrane antigen (PSMA), which is found on the surface of most metastatic prostate cancer cells. Therefore, actinium-225 not only treats bone, but also targets metastases in any tissue or fluid, even undetectable systemic micrometastases. Since it is an alpha emitter (very short range), it is less toxic to bone marrow or other nearby tissues. It is currently in the pipeline, and we hope it will be released soon.

Xgeva (denosumab) is given monthly to treat and to deter further bone metastases by blocking the protein known as RANK ligand inhibitor (RANK-L), which plays an important role in prostate cancer proliferation in bone. We are currently using denosumab in lower doses (Prolia®), given monthly for 6 months to help strengthen the bones in prostate cancer patients on ADT, and we are awaiting the outcome of trials using Xgeva monthly in patients having organ confined, high-risk non-metastatic prostate cancer.

There is also a lot of interest in combining immune therapies with other agents, drugs and radiation to make immunotherapy work better.

Looking back over the last five years, in addition to new drugs, we have seen some interesting trends. One we believe is the unfortunate byproduct of a recommendation made by the U.S. Preventive Services Task Force (USPSTF) that discourages men from getting routine PSAs and is predictably resulting in more men presenting with advanced cancer to lymph nodes and bone beyond the prostate gland than previously seen.

Yet another alarming trend is the dramatic increase in the number of men coming to us very shortly after having robotic surgery, reporting that their PSA never fell following surgery or if it did fall, it rapidly started to climb again. These are men who believed that robotic surgery would resolve their prostate cancer threat. These cases are not strictly "recurrence" but more correctly "persistence." Their initial, original treatment did not remove all of their prostate cancer, and a secondary treatment (radiation or

hormones or both) would be required. If we see these men early enough following surgery (the lower the PSA, the better) we have had good success in defeating their cancers, once and for all, utilizing "Salvage" Dynamic Adaptive Radiation Therapy (DART) to maximally avoid unwanted toxicities. Perhaps if we had seen them first, our combination radiation assault coupled with brachytherapy most likely would have totally eliminated their disease in the first place, and the patient could have been spared the side effects of surgery.

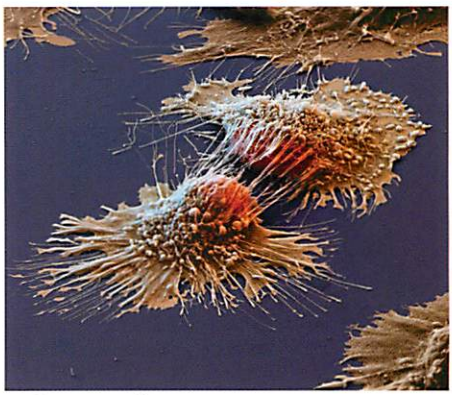
One encouraging observation of these patients with persistent disease is that the word is finally getting through to urologists and oncologists that as soon as the PSA starts to rise, the patient should be evaluated for further treatment. In the recent past, these men (the patients and their physicians) often waited until the PSA was up around 2.0 or higher before any action was taken. Today we know that if the PSA inches up to even 0.2, or two consecutive rises after surgery (even if less than 0.2), one should start considering further treatment (radiation and/or hormones).

So, what is in store for the man whose rising PSA following surgery signals the recurrence or persistence of his prostate cancer? The first thing is to verify the presence of disease and whether it is local (in the "prostate bed" – tissue left behind) or beyond the prostate or both. Newer, more sophisticated diagnostic technologies can determine the location(s) of recurrent/persistent malignancy.

WHAT IS THE "PSA BOUNCE?"

PSA Bounce or "flare" is a phenomenon experienced by about 30-40% of patients who have undergone prostate seed implants. It is a *temporary rise* in PSA occurring about 18-24 (range 6-36) months following implant, possibly caused by radiation induced prostatitis (inflammation of the prostate which may be subclinical – that is, asymptomatic) triggering a release of PSA. In approximately one-third of these cases, there is no prostate inflammation. This is not recurrence. The "bounce" seems to occur more often in younger men (55 years or younger), and in men of all ages who have larger prostate glands. The PSA bounce may subside with a course of antibiotics, alpha-blockers or anti-inflammatory medications, or it may just diminish naturally over time.

After a thorough review of the recurrent patient's history and current lab and imaging reports, ruling out "local" extension of the disease (meaning the immediate area outside the prostate gland), we may recommend an advanced lymph node screening exam, as well as screening for metastatic disease spread to bone and visceral organs. Prior to 2009, these men were sent to the Netherlands for a Combidex scan, which used nanoparticle technology to detect distant prostate cancer spread. For more than 5 years, we have been sending men with suspected "distant" metastatic disease for another nanoparticle test called "Feramoxytol" (Feraheme), which has high predictive accuracy in picking up on lymph node disease. This is most commonly coupled with an 18F PET/CT scan, a very exacting test detecting disease spread to bone. These nanoparticle tests are known as USPIO (ultra-small super paramagnetic iron oxide)



Cancer cells

CONTINUED ON PAGE 12

Recurrence: An Update

CONTINUED FROM PAGE 5

or Feraheme, referring to the radioactive isotope used in imaging. The method of action is the same. The patient is injected with the isotope one day, and the scan is performed the next day.

The isotope material used will "light up" the lymph chain and clearly indicate which nodes are harboring active prostate cancer cells. With this information, we can design precision DART treatment to address those specific lymph nodes and treat them to a high dose level. Since the test is based on advanced CT and MRI imaging, visceral metastasis to liver and lung can also be detected.

Another imaging test using Gallium-68 PSMA (Ga-68) is being investigated and has great promise. It attaches to PSMA on the surface of metastatic prostate cancer cells and can therefore detect bone, lymph node and visceral metastases with high predictive accuracy, even with low PSAs. Because Ga-68 is much more stable than C-11 Choline (which is short-lived and has to be made one dose at a time at select imaging centers as a PET/CT Choline + PET/CT Carbon-11 Acetate scans), Ga-68 PSMA test could be used at medical centers around the nation.

We have been collecting data on these cases, namely men having lymph node and boney disease spread, and we are preparing an article to report our success in treating patient subsets in an upcoming medical journal. We are working with the University of Washington in Seattle, and the preliminary results look extremely favorable. We are also partnered with Harvard University using yet another imaging agent, ^{18}F–Fluciclovine, more commonly known as an Axumin-Enhanced PET Scan, with impressive early results in picking up residual/recurrent disease within the prostate, lymph nodes, bones and visceral metastasis.

Beyond this direct approach with radiation and second-line hormonal therapies, there are new immunotherapy agents in the testing process which ramp up both B-cells and especially T-cells to attack prostate cancer cells. These are known as "check point inhibitors" and include a class of drugs called "PARP inhibitors" (e.g., Lynparza®) as well as anti-CTLA-4 (Yervoy®), and anti-PD-1/PDL-1 inhibitors (e.g., Opdivo® also known as Nirulmab®). These checkpoint inhibitors are currently being used in other cancers and have been FDA-approved for melanoma, lung and kidney cancer. Genetic testing is becoming increasingly important to select the right drugs for the specific tumor. We are hopeful that these checkpoint inhibitors will be "fast tracked" by the FDA, similar to the experience with Zytiga and Xtandi.

BE VIGILANT, ACT PROMPTLY

In conclusion, the message here is that all men who have had a prostate cancer diagnosis and have been treated with any method should be very vigilant in watching their PSA. The moment it starts to rise, extra concern should be given to the rise and finding out why it is rising. While drugs like Proscar® and Avodart® are known to reduce the PSA, many men take vitamins/supplements and change their diets and lifestyles following a prostate cancer diagnosis and treatment. This is a very good thing with the objective being to slow the rate of the PSA rise and improve general health. There is, however, the scenario whereby the PSA declines (without Avodart or Proscar), which may lull patients into a false sense of security. Some cancers may mutate, become more aggressive, no longer resemble the "parent prostate cell" and no longer be obliged to even make PSA! This is a great cause for concern. This phenomenon is even missed by some of the most astute oncologists.

Final note: Like early diagnosis, the best time to treat a recurrence is as soon as it is evident.