RECURRENCE
WHAT NOW!

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Five years ago, we published an article in the spring 2012 issue of Journey, (a "donors" publication from the Dattoli Cancer Foundation) 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 both 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® as well as many other exciting and novel immunotherapeutic agents, which hopefully will soon to be "fast tracked" by the FDA to the marketplace. [1-2]

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 which has spread to bones. Not only does Xofigo® relieve bone pain, but it 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, other injectable isotopes called Actinium-225 (alpha emitter) and Lutetium-177 (beta emitter) attach to prostate-specific membrane antigen (PSMA). PSMA is found on the surface of most metastatic prostate cancer cells. Therefore, these newer isotopes treat not only bone, but can target metastases in any tissue or fluid, even undetectable systemic micro-metastases. Since they are alpha and beta emitters (very short range), there is far less toxicity to bone marrow or other nearby tissues. Lutetium-177 is currently being used investigationally while Actinum-225 is in the pipeline and we hope it will be released soon.[3]

Xgeva® (denosumab) is a subcutaneous injection given monthly to treat and to deter further bone metastases by blocking the glycoprotein known as RANKL (receptor activator nuclear factor ligand) which plays an important role in prostate cancer proliferation in bone. This is used in prostate cancer patients having documented spread to one or more bone sites. In this setting, patients receive 12 consecutive months of Xgeva® and then enter a 3 month holiday. We are also currently using denosumab in patients without skeletal metastases in lower doses (Prolia®) given once, every 6 months to help strengthen the bones in prostate cancer patients who are on ADT with the added potential benefit of deterring metastatic bone spread. Meanwhile we are awaiting the outcome of trials delivering Xgeva® monthly in patients having organ confined, high-risk non-metastatic prostate cancer.[4]

There is also a lot of interest in combining immune therapies with other agents, drugs and especially radiation. Combining radiation with immunogenic drugs has great promise since the effects of the body's immune response to cancer is enhanced.[5] These immunogenic synergistic effects of radiation and immunogenic drugs (especially "check point" inhibitors and PARP inhibitors, to be discussed later, and even Zytiga® and Xtandi®) are thought to result from 'autovaccination' by antigens released from dying cancer cells and fragmented, damaged DNA. Mechanistically, radiation (all types, even Xofigo®) has been shown to augment the afferent, as well as the efferent arms of cancer immunity. The induction of a positive T-cell response against cancer has been observed in numerous studies.[6]

Looking back over those 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) in 2012 that has discouraged men from getting routine PSA's, and is predictably resulting in more men presenting with advanced cancer to lymph nodes and bone beyond the prostate gland than previously seen.[7] Yet another alarming trend is the dramatic increase in numbers 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 soon began to climb again and did so rapidly in many cases. These are men who believed that robotic surgery would resolve their prostate cancer threat with lesser side effects than conventional prostatectomy ("open retro-public"). 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) is 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 to neighboring critical organs and structures. 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. Nonetheless, surgery remains an option in select patients following advanced diagnostic staging.

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 +/- hormones). Recognize that prostate recurrence following surgery may be comprised of high grade, mutated, undifferentiated cancers which bear little resemblance to the "parent prostate cell." In view of this, they often flourish and yet produce minimal amounts of PSA.

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. Is it still in the prostate bed and/or has it traveled to the lymph nodes or bone?

...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.

WHAT IS THE "PSA BOUNCE"

PSA Bounce or "flare" is a phenomenon experienced by about 30-40% of patients who have undergone prostate brachytherapy (seed implants) and 10-20% of patients receiving temporary High Dose Rate prostate brachytherapy.[8] While the most thoroughly analyzed patients are those having permanent seed implants, it has also been reported to occur in patients having undergone prostate irradiation alone to high dose level and we are even seeing this phenomenon occur in patients undergoing nodal radiation. 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 clinical and associated with prostate symptoms, or subclinical – that is, asymptomatic) triggering a release of PSA.

Interestingly, 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 having larger prostate glands. The PSA bounce may subside with a course of antibiotics or alpha-blockers or anti-inflammatory medications, supplements or it just diminishes naturally over time.[9]

I believe that I may hold the world record for the highest "benign PSA bounces." I performed brachytherapy on a 45 year old male from Ireland approximately 15 years ago and later his PSA increased to as high as 28.6! Urologists hovered over him wanting to remove his prostate. They didn't (this took a lot of convincing) and now, 15 years later, his PSA is undetectable.

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 viscera 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 to pick up on lymph node disease. This is most commonly coupled with an ^{18}F PET/CT scan, a very exacting test detecting disease spread to bone. These nanoparticle tests are known as USPIO scans (ultra-small super paramagnetic iron oxide) or Feraheme, referring to the reagent used in imaging. The method of action is the same. The patient is injected with the reagent one day, and the scan is performed the next day.[10]

The reagent used will "light up" the lymph chain and clearly indicates which nodes are harboring active prostate cancer cells. With this information, we can design precision DART treatments 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.

Other advanced imaging tests include PET/CT C-11 Choline and PET/CT Carbon Acetate C-11 scans. Aside from nanoparticle imaging, other functional and molecular imaging is being carried out. For example, Gallium-68 PSMA (Ga-68) is being investigated and has great promise. It attaches to PSMA which is 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 PSA's. 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), Ga-68 PSMA test could be used at medical centers around the nation.

Meanwhile, 3D color Flow Power Doppler Ultrasonography (used at our Center and a few select centers worldwide) can pick up intra-prostatic cancer recurrence. I have personally reseeded up to 1,000 patients with intact prostates, with great success and limited morbidity. This is referred to as "salvage" prostate treatment (either partial prostate or entire prostate). Other potential options include, but are not limited to, cryoablation (freezing), HIFU (heating), biothermy (freezing and heating), Nanoknife (irreversible electroporation) and focal MRI guided interstitial ablation. Each has its own benefit and side-effect profile.

Any of the above can treat the entire prostate gland or a portion of the gland (i.e. partial treatment). Partial treatment should never ever be recommended as initial treatment and should only be considered as salvage therapy. Similar to breast cancer, prostate cancer is also a "field effect" disease. That is, what has happened at one or several locations, will occur elsewhere in the gland since all cells have been subject to the same environmental cues and genetic predilections. This will lead to multiple future focal

treatments and greatly increased morbidity. Additionally, more traditional and effective salvage therapies will be compromised in patients having initial partial treatments.

Most patients who recur in the prostate gland will be identified to have spread to other sites following careful re-staging. Even if the re-staging proves negative, I most often combine salvage re-seeding along with DART to relevant nodal chains, as the possibility that lymph nodes harbor microscopic cancer. To date, even the most sophisticated, advanced diagnostic tests cannot pick up microscopic disease.[11-12]

We have been collecting data on these cases, namely men having lymph node and boney disease spread, and we are in the process of preparing an article to report our success in utilizing Feraheme and other functional and molecular imaging tests to denote lymph node spread as well as 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 advanced imaging test, ^{18}F – Fluciclovine, more commonly known as an "Axumin-Enhanced PET Scan," with impressive early results picking up residual/recurrent disease within the prostate/prostate bed, lymph nodes, bones and visceral metastasis.

Beyond this direct approach with radiation and 2nd-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 broadly known as "check point inhibitors" and encompass a class of drugs including anti-PD-1/PDL-1 inhibitors (e.g. Opdivo® also known as nivolumab, etc.) as well as anti-CTLA-4 (Yervoy®). These immune checkpoint inhibitors are currently being used in other cancers and have been FDA-approved for melanoma, lung and kidney cancer.

Genetic testing, (especially BRCA1/BRCA2 in prostate cancer) is becoming increasingly important, as is molecular profiling, to select the right drugs for the specific tumor. A recent survey from Memorial Sloan-Kettering Cancer Center suggests that immunotherapy agents for prostate cancer show enhanced benefits when utilized in combination with various biologic agents, chemotherapies, and radiation.[13] For example, patients having BRCA2 mutations most commonly respond to yet another group of novel drugs called PARP inhibitors (poly ADP-ribose polymerase) to help determine if patients will respond to the immune drug Lynparza®. We anxiously await the release of the PARP inhibitor drug Lynparza® for patients who are initially resistant to Zytiga® or Xtandi®, or who become resistant over time. Meanwhile a test analyzing serum called "droplet digital PCR assay" can help determine patients who will best respond to Zytiga® and Xtandi®. The biomarker Androgen Receptor Splice Varient-7 (AR-V7) expression in tissue, and more recently in blood, could predict resistance to Zytiga® and Xtandi®, although it could help personalize checkpoint inhibitors, or possibly even chemotherapy more specifically designed for the tumor.[14-15] We are hopeful that these checkpoint inhibitors and other novel therapies are "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, velocity and doubling time, and to improve general health. There is, however, the scenario, especially with "Active Surveillance" whereby the PSA declines (without Avodart® or Proscar®) which may lull patients into a false sense of security. As previously described in patients following surgery, this is the case since some cancers may mutate, become more aggressive, no longer resemble the parent prostate cell and are no longer obliged to even make PSA! This is a great cause for concern. This phenomenon is even missed by some of the most astute urologists, oncologists, and even some prostate oncologists.

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

Citations:

1. Phase II clinical trials of Prostavac® with hormone-resistant patients have shown increased overall survival of 8.5 months and a 44% reduction of death rate Kantoff PW, J Clin Oncol. 2010 March 1;28&7):1099-105
2. Kanoff PW, J Clin Oncol. 2017 Jan;35(1):124-125
3. Kratochwil C, et al, 225Ac-PSMA-617 for PSMA targeting alpha-radiation therapy of patients with metastatic castration-resistant prostate cancer, J Nucl Med July 7, 2016
4. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: Results of a phase 3, randomised, placebo-controlled trial, smith MR, et al, Lancet. 2012 Jan 7:379(9810):39-46
5. Golden EB, et al Semin Radiat Oncol. 2015:25 (1) 7-11
6. Kapoor A, et al, Contemporary agents in the management of metastatic castration-resistant prostate cancer, Can Urol Assoc J. 2016 Nov-Dec;10(11-12):E414-E423
7. Recent changes in prostate cancer screening practices and prostate cancer epidemiology, Lee DJ, J Urol. 2017 May 25
8. Makarewicz R, et al Jour Cont Brachy. 2009: 1(2) 92-96
9. Prostate-specific antigen bounce predicts for a favorable prognosis following brachytherapy: a meta-analysis, Bernstein MB, et al, J Contemp Brachytherapy: 2013 Dec; 5(4):210-4
10. Bravo SM, Dattoli MJ, Myers CE, et al; Safety and Efficacy of Feraheme as a Lymphatic Contrast Agent, ASTRO Symposia, Atlanta, GA Oct. 2013
11. Gallium-68 Prostate-Specific Membrane Antigen PET Imaging, Hofman MS, PET Clin, 2017 Apr;12(2):219-234
12. [68Ga] DKFZ11-PSMA Pet Scans for Detecting Prostate-specific Membrane Antigen-positive Prostate cancer. Osborne JR, et al, Mol Imaging Biol, 2017 May 22
13. Immunotherapy in metastatic prostate cancer, Slovin SF, In J Urol. 2016 Oct-Dec;32(4):27-276
14. Clinical Significance of Androgen Receptor Splice Variant-7 mRNA Detection in Circulating Tumor Cells of Men with Metastatic Castration-Resistant Prostate Cancer Treated with First- and Second-Line Abiraterone and Enzalutamide, Antonarakis ES, et al, J Clin Oncol. 2017 Apr 6
15. Association of AR-V7 on Circulating Tumor Cells at a Treatment-Specific Biomarker with Outcomes and Survival in Castration-Resistant Prostate Cancer, Scher HI, et al, JAMA Oncol. 2016 Nov 1;2(11):1441-1449