ADVANCED PROSTATE CANCER/HIGH GLEASON SCORE AT DIAGNOSIS?

by Charles (Chuck) Maack – Prostate Cancer Activist/Mentor

DISCLAIMER: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued research and study in order to serve as an advocate for prostate cancer awareness, and, from a activist patient's viewpoint, to voluntarily help patients, caregivers, and others interested develop an understanding of prostate cancer, its treatment options, and the treatment of the side effects that often accompany treatment. There is absolutely no charge for my mentoring – I provide this free service as one who has been there and hoping to make your journey one with better understanding and knowledge than was available to me when I was diagnosed so many years ago. Readers of this paper must understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as my opinion, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing your prostate cancer care.

If you have JUST been diagnosed with high grade, advanced, prostate cancer already known to have metastasized - RECENTLY (JAN 2014) results from the CHAARTED trial recommends a combination of hormonal medications accompanied by a series of chemotherapy with docetaxel/Taxotere for men diagnosed with high grade and metastasized prostate cancer. Please review the following and discuss with your treating physician who, if not a Medical Oncologist, should bring a Medical Oncologist on board for additional consultation and treatment:

http://tinyurl.com/q7e7a2g and another paper from the STAMPEDE study http://tinyurl.com/q3x6eve

You may want to consider joining an online advanced prostate cancer support list, if you have not already, where you can interact with other patients, caregivers, and mentors who are or have already travelled in this journey and where you can learn from their experiences. See:
https://groups.yahoo.com/neo/groups/advancedprostatecancer/info

The following are recommendations that are important BEFORE considering whether radiation or surgery should be administered. They should be used to establish baseline markers in developing a strategy of treatment. Both radiation and surgery should be held in abeyance with high Gleason Score patients until it is determined whether or not their cancer has migrated beyond the gland. Gleason Scores of 4 + 3/7, 8, 9, and 10 are considered high range. Gleason Score 4 + 3 cancers are associated with a three-fold increase in lethal prostate cancer compared with 3 + 4 cancers. Radiation and surgery are often suggested to "debulk" the amount of cancer that would still require other treatment options, but there are specialists who consider surgery an aggravation of the prostate gland that, when administered to a patient with extensive tumor presence and the likelihood of extension beyond the gland, could result in more harm than good. Yet, there is a study released on 5/13/11 by Mayo Clinic indicating there can be an 80% chance of up to 20 years survival with surgical removal of the gland for men diagnosed with advanced prostate cancer. And, patients should be aware that there are studies that external beam radiation therapy, even for localized prostate cancer (PC), may be linked to bladder, lung and colorectal cancer. For the latter, review the following URLs:
http://tinyurl.com/oryrynb
http://www.medicalnewstoday.com/articles/107505.php
http://tinyurl.com/ygkbzkv

So much about which to be concerned! I think it would behoove any patient initially diagnosed with the foregoing Gleason Scores to consider the following imaging to identify metastasis locations

C-11 CHOLINE PET/CT IMAGING or C-11 SODIUM ACETATE PET/CT IMAGING:

Please review info here: http://tinyurl.com/by49gqo

With diagnosis of advanced/high Gleason Score PC, you should also consider bringing in a Medical Oncologist along with your Urologist to oversee your care. If metastasis has not yet been determined, one or the other should be testing your PAP, CGA, NSE, and CEA levels to determine PC aggressiveness, and preferably before starting any treatment method. These tests and what they may indicate are explained in the "PAP, CGA…" URL here: http://tinyurl.com/cbdw5lc . Testing should also include a Chemistry Panel/Complete Blood Count (CBC). **Also, check fasting prolactin level since prolactin SENSITIZES the AR (androgen receptor) and also inhibits Dopamine thus favoring angiogenesis.** If the fasting prolactin is 5.0 or higher, start Dostinex (cabergoline) at 0.25 mg three times per week (further explained here: http://tinyurl.com/7w5omeo). A month later recheck the prolactin level. These tests along with a most current PSA and Testosterone (T) level then provide the necessary baseline markers to develop treatment strategy.

Here are specific recommendations in this regard provided to a patient with several biopsy results (primarily of Gleason Scores of 4,4 but also of 4,3 with tertiary presence of Grade 5) by internationally renowned Medical Oncologist Stephen Strum, specializing specifically in research and treatment of advanced prostate cancer since 1983:

"<Stephen Strum, MD>
This is high volume PC of an aggressive histologic type (mostly GS (4,4) & (4,3) along with PNI (perineural invasion) which is a risk factor for EPE (extra-prostatic extension) along with the fact that EPE was actually seen. This is not the kind of clinical situation that I would be thinking about doing a local procedure without first obtaining sophisticated staging studies to determine the extent of the disease. And, most probably, these biopsy findings are consistent with systemic spread of PC to bone and/or nodes. Thus, the burden of proof on any physician evaluating you is to rule out the presence of non-confined PC. Such studies in this context would include, in my opinion, the following prior to any local procedure:

1. PAP, CGA (Chromogranin A), NSE (Neuron Specific Enolase), CEA (Carcinoembryonic Antigen) blood tests in light of the high Gleason score. See page 64 of The Primer on Prostate Cancer by Strum & Pogliano for discussion of these other blood test biomarkers.

2. Of course DRE (digital rectal exam) but also findings of TRUSP (transrectal ultrasound of the prostate) in relation to involvement of capsule and seminal vesicle.

3. 3T MRI of the prostate but this would need to be done either before the biopsies due to artifact caused by biopsy induced bleeding or 2 months after the TRUSP with biopsies. (My note: The more advanced and sensitive 3T multiParmetric imaging is now available at various locations as well as the Stephenson Cancer Center, University of Oklahoma Health Sciences Center. Call (405) 271-1333 for further information, appointment, and directions.)

4. Evaluation of bone and nodes using MRI of the axial skeleton (spine, pelvis, long bones). (for those relatively close to an imaging center that provides 3T multiParametric imaging, I would recommend that consideration.)

5. Assessment of bone resorption since abnormalities more often found in patients with systemic spread of PC. This would include DpD (deoxypyridinoline) urine test along with a blood bone resorption test such as b-CTX (C-Terminal Telopeptide, b-Crosslaps) or amino-terminal procollagen propeptides of type I collagen (PINP). Also, bone density using quantitative computerized tomography (QCT) and definitely NOT using DEXA which will falsely elevate bone density if osteoarthritis or vascular calcium deposits which almost every man over the age of 60 will have."

Once these tests have been administered, and while determining a treatment option, I believe you should then be prescribed androgen deprivation therapy (ADT) that include an antiandrogen (Casodex or its generic bicalutamide, flutamide/Eulexin, or nilutamide/Nilandron), and LHRH agonist (Lupron, Zoladex, Eligard, Trelstar, or the antagonist Degarelix), AND a 5AR inhibitor (dutasteride/Avodart preferred, or alternatively finasteride/Proscar) ASAP. Medical Oncologist Strum comments: "I personally have been involved with ADT (androgen deprivation therapy) since 1983 and was one of the first investigators for ADT in the world, working as a co-investigator with Fernand Labrie. I would be using a 5ARI (5-alpha reductase inhibitor) such as Avodart in conjunction with the above agents. I also would have

checked a prolactin blood level and if 5 or higher would lower it with a drug such as Dostinex. In addition, it is critical to obtain serum testosterone levels to assure that there has been sufficient androgen deprivation (AD) achieved by the therapy being used. Given that ADT causes bone loss by activating osteoclasts, I would be using Zometa + a comprehensive bone supplement immediately." (With the more recent availability of a new alternative to infusing Zometa, the medication denosumab/Xgeva is being prescribed since it is an every-four-weeks subcutaneous injection rather than going through the infusion process of Zometa. The comprehensive bone supplement I would recommend is DR. STRUM'S INTENSIVE BONE FORMULA – read information and orderin at http://tinyurl.com/ovnhbj5.

If prescribed an LHRH agonist, be certain that your physician starts you on an antiandrogen first (bicalutamide/Casodex 50mg one tablet daily most usually now prescribed) to prevent a side effect that could otherwise occur known as "flare" and explained here: http://www.theprostateadvocate.com/pdf/FLARE.pdf , (pre-antiandrogen not required if prescribed the GnRH antagonist Firmagon/degarelix). AND include a 5Alpha Reductase (5AR) inhibitor (dutasteride/Avodart 0.5mg one capsule daily my choice) to inhibit T conversion to dihydrotestosterone (DHT) to begin a week prior to administration of the first LHRH agonist injection (most likely Lupron but many also using Zoladex Eligard, or Trelstar) and to be continued while also prescribed the LHRH agonist. The reasoning for this sequence of medication administration and the specific performance of each medication is explained in the "Triple Hormonal Blockade" paper here: http://tinyurl.com/3ulagd2**.** (As previously noted, if the GnRH antagonist degarelix/Firmagon is prescribed, the antiandrogen can begin with the first injection of this medication, since its action has been found to not cause a "flare" reaction). In the prescribing of Lupron, Dr. Strum, recommends that the initial injection be at only 7.5mg (or the lowest dosage depending on the LHRH medication employed) that is effective for 28 days be first employed and that at about 3 weeks, a blood draw administered to determine that this therapy is working with your PSA level having drastically dropped into the ultrasensitive levels and your testosterone level also dropping significantly. This provides the indication that your cancer remains androgen "dependent" and this therapy will work. This 7.5mg injection then continues for another 28 days until your PSA drops to <0.05ng/ml and your testosterone to <=20ng/dl which indicates the ADT is working appropriately. (If this is not occurring, then your cancer may be androgen independent and requires an entirely new strategy of treatment). If the PSA and T levels have dropped as indicated, the injection can change to either the 22.5mg 3

month effective or 30mg 4 month effective or more recently the 45mg 6 month effective. I personally do not advocate implant of a 12-month LHRH agonist. I doubt that the medication actually remains fully efficient for the entire twelve months. I am even suspect that the so-called 4 or 6 month injections are fully effective for that length of time (just a personal opinion). And at the blood draws after a few months on ADT3, testing for DHT level should also be included with the PSA and T checks, since the 5AR inhibitor should have brought the DHT level down to <10.0ng/dl. This is all explained in the foregoing URL. Also, a thorough explanation with supporting references of the importance of a 5Alpha Reductase (5AR) inhibitor (dutasteride/Avodart (my preference) or finasteride/Proscar) as part of triple androgen/hormonal blockade (ADT3) can be reviewed here: http://tinyurl.com/3gfd23r . Read "ADT Side Effects") for explanation of the side effects that might occur with ADT and how to combat those effects here: http://tinyurl.com/3p9pl3p . Also to be considered to image cancer volume and location would be the C-11 Choline PET imaging, the USPIO imaging, Color Doppler Ultrasound (CDU), as well as 3T multiParametric MRI. If there are indications of metastasis despite no solid evidence, a series of chemotherapy with weekly docetaxel/Taxotere (that could be accompanied by carboplatin, an estradiol like estramustine/Emcyt, or other estrogen) to accompany androgen deprivation therapy could also be considered as part of an all out attack to stop continued development and hopefully eradicate the cancer. As a PC friend with Gleason 10 suggested, men with advanced prostate cancer should put on war paint, gather all their ammunition, and attack from every direction with everything available.

You should also be given bone mineral density (BMD) imaging with preferably a Quantitative Computerized Tomography (QCT) imaging, or at least a Dual-Energy X-ray Absorptiometry (DEXA) imaging (this is different than the bone scan checking for metastasis). A good idea is to also have your bone integrity checked with a Pyrilinks-D Dpd deoxypyridinolene urine test and/or b-CTX (C-Terminal Telopeptide, b-Crosslaps). These tests are important because very often at diagnosis with prostate cancer, men are also experiencing osteopenia or osteoporosis. And particularly if bone metastases is considered possible or known, then beginning the bisphosphonate Zometa or Xgeva for bone protection. And particularly with starting on androgen deprivation, this testing should be part of developing base marks for the strategy of treatment. The reasoning for "QCT BMD Imaging vs DEXA BMD Imaging" is explained here: http://tinyurl.com/7ewmovu . If it is determined that osteopenia or osteoporosis is developing or just to protect bone from metastases the prescribing of

bisphosphonates is being discussed, a description of **"**Bisphosphonates & Dental Considerations" is described here: http://tinyurl.com/3m78ymg

Also, a lengthy compilation of information regarding "Diet and Supplement Considerations in our Fight Against Prostate Cancer" can be reviewed here: http://tinyurl.com/6z5l8fm .

Those with high grade prostate cancer at diagnosis and considering either surgery or radiation that would be more so to debulk the amount of cancer, should take the below suggestion to their physician as well as find and discuss with a Medical Oncologist prior to any plans for surgery or radiation to discuss pre-surgery/pre-radiation treatment with chemotherapy agents docetaxel/Taxotere and mitoxantrone for the possibility of a better chance of recurrence free survival.

See: http://www.ncbi.nlm.nih.gov/pubmed/20143429 **Cancer 2010 Feb 8 {Epub ahead of print}**

Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer.

Garzotto M, Higano CS, O'Brien C, Rademacher BL, Janeba N, Fazli L, Lange PH, Lieberman S, Beer TM.

Division of Urology, Oregon Health and Science University, Portland Veterans Administration Medical Center, Portland, Oregon.

BACKGROUND:: A study was conducted to determine the 5-year recurrence-free survival in patients with high-risk prostate cancer after neoadjuvant combination chemotherapy followed by surgery. Secondary endpoints included safety, pathologic effects of chemotherapy, and predictors of disease recurrence. METHODS: Fifty-seven patients were enrolled in a phase 1/2 study of weekly docetaxel 35 mg/m(2) and escalating mitoxantrone to 4 mg/m(2) before prostatectomy. Patients were treated with 16 weeks of chemotherapy administered weekly on a 3 of every 4 week schedule. A tissue microarray, constructed from the

prostatectomy specimens, served to facilitate the exploratory evaluation of biomarkers. The primary endpoint was recurrence-free survival. Disease recurrence was defined as a confirmed serum prostate-specific antigen (PSA) >0.4 ng/mL. RESULTS: Of the 57 patients, 54 received 4 cycles of docetaxel and mitoxantrone before radical prostatectomy. Grade 4 toxicities were limited to leukopenia, neutropenia, and hyperglycemia. Serum testosterone levels remained stable after chemotherapy. Negative surgical margins were attained in 67% of cases. Lymph node involvement was detected in 18.5% of cases. With a median follow-up of 63 months, 27 of 57 (47.4%) patients recurred. The Kaplan-Meier recurrence-free survival at 2 years was 65.5% (95% confidence interval [CI], 53.0%-78.0%) and was 49.8% at 5 years (95% CI, 35.5%-64.1%). Pretreatment serum PSA, lymph node involvement, and postchemotherapy tissue vascular endothelial growth factor expression were independent predictors of early recurrence. CONCLUSIONS: Preoperative chemotherapy with docetaxel and mitoxantrone is feasible. Approximately half of the high-risk patients remain free of disease recurrence at 5 years, and clinical and molecular predictors of early recurrence were identified. Cancer 2010. (c) 2010 American Cancer Society.

PMID: 20143429 [PubMed - as supplied by publisher]

Finally, a list of "Books" that every man diagnosed with prostate cancer should consider adding to his home library can be reviewed here: http://www.theprostateadvocate.com/pdf/BOOKS.pdf .

I don't mean to overwhelm you with this information but more to make you aware that these tests and treatment methods are important and your physicians should be considering them while developing an appropriate strategy for your future treatment. If he/she discounts these tests, you might consider moving to Urologists and Medical Oncologists who understand their value.

Physicians (including Urologists/surgeons, Radiation Oncologists, Pathologists, and Medical Oncologists who are often spoken of by many patients and colleagues as having special expertise in the testing, imaging, and treatment of prostate cancer are listed here: http://tinyurl.com/3w94mtc

Much of the information in the foregoing can be found at http://pcri.org/pcri-papers/

REMEMBER: I am always as close as the other end of your computer to help address any prostate cancer concerns.