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Contents

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AN EDITORIAL: PSA Screening For Prostate Cancer

"Don't throw out the baby with the bath water" - don't forget the many men still being diagnosed with more advanced cancer by PSA testing. Men tuned in to the current screening debate could easily get the erroneous impression that most, if not all, patients are now diagnosed with inconsequential and slow-growing prostate cancer.

In the raging debate about whether to screen or not, the nay-sayers, with their ever increasing and vocal admonitions, by now ought to be penalized for "piling on". Virtually no man has been spared from repeated proclamations that the PSA test is inefficient, useless, and, in fact, likely harmful. From a clinician's point of view, what is glaringly missing from these dismissive negative vibes, other than the requisite plea that "better markers" are needed, is a "plan B" to avoid a return to the "bad old days" of the "DRE only" when a diagnosis awaited palpably advanced local disease, or even worse, when symptoms of metastatic disease announced an incurable condition.

CASE IN POINT: Having had his first PSA at age 66, one man's PSA fluctuated in the next three years between 4.8 ng/ml and the high 5s. Then came a 6.2 ng/ml resulting in a confirmatory follow-up test several months later showing 7.9 ng/ml. He is asymptomatic; and the gland size is ~80 cc. A thirteen-core biopsy showed a small portion of one core with Gleason 4+4. The Partin Table estimation for extra-capsular extension is in the mid 40% range. *Because* the diagnosis was made at this stage in his disease he has the choice of good options for initial treatment and a reasonable likelihood of a good

long-term outcome. How much poorer his chances would have been several years later if diagnosed because of a grossly abnormal gland or, worse, a painful spinal metastasis!

The critics of screening rightly cite the stage migration that in recent years results in >70% of men having low volume, low-risk disease. The results of early intervention of any sort at this stage piggybacks onto the indolent natural history of this disease presentation to produce very favorable long-term (often >90% at 15 years) control or cure. It is data of this sort that fuels the debate about over-diagnosis and over-treatment.

Urologists and radiotherapists, however, need no reminder that, despite the trend to lower-stage and lower-risk prostate cancer, a considerable number of men still present with locally advanced disease and worrisomely high PSA levels and Gleason scores. They appreciate that a primary care physician or internist drew a PSA test, knowing that in its absence a diagnosis later in the course of the disease would have resulted in diminishing options for optimal outcome.

If there is any question about the prevalence of advanced cancer in newly diagnosed patients, consider the characteristics *at diagnosis* of men in the European Randomized Study of Screening for Prostate Cancer shown in Supplementary Appendix 6, NEJM, March 2009:

In the screening arm were 5990 men, and controls numbered 4307. For T-Stage in the screening vs. control groups: T1c, 57% v 41%; T2, 29% v. 30%; T3, 8% v. 17%, and for T4, 1% v. 3%, respectively. In the T3/T4 grouping this data represents a 22% reduction in advanced cancers in the screened men.

As regards Gleason score comparisons, screened v. control: Gleason 2 - 6 , 59% v. 35%; Gleason 7, l7% v. 18%; and for scores >7, 6% v. 10%. Metastatic disease (M1) at diagnosis showed a 41% reduction in the screened group: 149/5990 = 2.5% v. 304/4307 = 7.1%.

Considering that more than 190,000 men may be diagnosed with prostate cancer in 2010, this data for the prevalence of T3/T4 and metastatic disease at diagnosis is sobering.

Speaking directly to the major point of this editorial is "Risk of Dying From Prostate Cancer in Men Randomized to Screening: Difference Between Attendees and Nonattendees, by Bergdahl et al., Cancer Dec 15,2009. The report focuses on 9972 men invited to participate in a Swedish screening study with PSA testing every 2 years. Prostate biopsies were recommended for a PSA >3 ng/ml (later >2.5). "Non-attendees" consisted of the 2394 men who were invited but chose to entirely avoid screening. "Attendees" were tested at least once, but many as often as seven times. Over the course of the 13 year study a total of 39 men died of prostate cancer.

"Twelve of the 15 deaths that occurred among complete attendees [were in men] whose *disease was detected at the time of the first screen"* (Italic mine) If those 12 are not included in the analysis, then "Only 6 men participating in regular screening died from prostate cancer," 3 of whom did not follow the protocol.

Among nonattendees 16 men died of cancer. These deaths occurred earlier in the study, with the trend becoming evident 2 years after randomization. "Nonattendees also *had more advanced cancer at the time of diagnosis," i.e.* higher median PSA values; and 15 of these 16 belonged to the high-risk group.

BOTTOM LINE: Caveat Emptor! Before abandoning PSA testing, let's be sure a "plan B" is securely in place to ensure the earliest possible diagnosis of prostate cancer so as to preserve options for men who need and will benefit from treatment.

CASTRATE RESISTANT PCA: MDV-3100, A Third Generation Anti-androgen: Available on Protocol

Men with progressive castrate-resistant prostate cancer (CRPC), having obtained maximal benefit from chemotherapy, are left with few promising therapeutic options. Fortunately, through the NCI Clinical Trials Program, a phase III study of oral MDV-3100 (Medivation, Inc.) is available on protocol for these

men. This multinational study is randomized, double-blinded, and placebo controlled. Early experience with the drug has been encouraging.

Results from a phase 1-2 trial of MDV-3100 were first reported at the December, 2009, meeting of the Society of Urologic Oncology. "All study patients had prior ADT and 54% had prior chemotherapy;" half had metastases. "62% of chemo-naive patients had a >50% decline in PSA, and 51% of chemo-exposed patients had a >50% decline in PSA. PSA progression in these two groups occurred at a median of 47 weeks and 28 weeks, respectively."

This major development, now reported in full in an Early Online Publication from Lancet, April 15, by Drs. Howard Scher, Higano, Beer et al. offered more details from the 140 man study: notably a >50% decline in PSA; a 22% response in soft tissue disease; bone disease stabilization in 56%; and 49% of men showed a "conversion to favorable circulating tumor-cell counts." The median time to radiologic progression was 47 weeks.

MDV-3100 is functionally superior to the anti-androgen, bicalutamide. Whereas bicalutamide is 30-fold weaker in androgen receptor (AR) binding than the natural ligand, dihydrotestosterone, MDV-3100 is only 2-3 fold less avid. Tighter bonding results in greater AR inhibition. MDV-3100 was specifically designed to function in the setting of CRPC wherein the androgen receptor is amplified, making current non-steroidal anti-androgens less effective. Both bicalutamide and flutamide carry the liability that over time they can become partial *agonists* of the AR. MDV-3100 has no agonist properties. In the presence of MDV-3100, mutationally altered androgen receptors are not activated by other steroid ligands, such a progesterone. Similar to other anti-androgens, MDV-3100 impairs nuclear translocation of the AR and AR transcription; and MDV-3100 *adds co-repressers*, not co-activaors, to the transcription machinery. (The development of MDV-3100 was reported in SCIENCE 8 MAY, 2009. http://www.sciencemag.org/cgi/content/full/sci;324/5928/787?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=MDV3100&se.)

At the University of Washington, the MDV-3100 protocol is sponsored by Dr. Evan Yu, who would manage MDV-3100 usage and follow-up of a referred patient in the study period. Standard medical care remains in the the hands of the referring physician. The Study Coordinator for this trial at the UW site is Shwetal Ahire: phone, 206-288-2045; e-mail, sahires@uw.edu. Eligibility details can be found at http://clinicaltrials.gov/ct2/show/NCT00974311?term=MDV3100&;rank=2.

DIET AND PREVENTION: Dietary Omega-3 Fatty Acids and Prostate Cancer

The benefits for men with prostate cancer of consuming a diet rich in omega-3 fatty acids and fish are highly touted - especially a diet rich in salmon, tuna, and sardines, fish that contain the greatest quantity of long-chain, polyunsaturated omega-3 fatty acids (FA). This subject was covered in Feb/March PCa Commentary, 2006. It seemed timely to review research reported since 2006 to see if the data supporting this beneficial association have strengthened.

The pertinent clinical results cited in the earlier article included:

1. A 2001 Lancet report with 30 years of follow-up documenting that Swedish men who ate no fish vs. those eating moderate to high amounts had a two- to three-fold higher frequency of prostate cancer;
2. A Harvard/NCI study of 47,866 men with 14 years of follow-up that found those men who consumed the highest vs. the lowest amount of fish had an 11% overall reduction of prostate cancer; and a 26% risk reduction for metastatic disease and
3. A Health Professionals Follow-up Study which reported that men with prostate cancer who ate the highest vs. the lowest amount of fish showed a 27% risk reduction of cancer progression.

Recent research has afforded a better understanding of the mechanisms underlying this link between fatty acids and cancer. This biology was succinctly reviewed by Ablin and Jiang in a JOURNAL OF UROLOGY editorial, January 2010, "All Fats are Not Bad."

First, a brief primer: There are two series of essential fatty acids. Omega-6 fatty acids are mainly found in meat. They are long-chained (20 carbon molecules), but have only two double-bonds. Omega-3 fatty acids (18-22 carbons) are highly unsaturated with 5-6 "unsaturated" bonds, and are generally toxic to cancer cells. Alfa-linolenic fatty acid (ALA) with 3 double-bonds, is also in the omega-3 series. It is obtained only from plant sources and is found naturally in walnuts, flax seed, soy, canola oil, and wheat germ. ALA can be converted into the more unsaturated omega-3 fatty acids, but only at a rate of less than 10%. Hence the best source of the desired omega-3s is from fish. In general, studies have shown that omega-6 FA promote growth of prostate cancer cell lines, whereas omega-3s are growth inhibitory.

Ablin points out that the toxicity of the two major long-chain omega-3s (DHA and EPA) may result from a lack in cancer cells of the enzymes needed to metabolize these molecules with the consequence of a build-up of toxic reactive oxygen species. Additional studies indicate that the polyunsaturated fatty acids "regulate the expression of tumor suppressor genes and in so doing impact the cell cycle and apoptosis"; beneficially regulate cell adhesion and communication molecules; and are "strong angiogenic inhibitors".

The article by Aronson et al. coupled with Albin's editorial presents persuasive results from a combined clincial/in vitro study: "Growth Inhibitory Effect of Low Fat Diet on Prostate Cancer: Results of a Prospective, Randomized Dietary Intervention Trial in Men With Prostate Cancer". The trial compared patients randomized between those who followed a "low fat (15% kcal), high fiber, soy protein supplemented diet or a 'Western' (40% kcal fat) diet for 4 weeks." LNCaP prostate cancer cells were exposed to pre-intervention and post-intervention serum "to assess the in vitro effect of the diet on prostate cancer cell proliferation". The serum from the low-fat group significantly decreased cell growth compared to the Western diet. Their analysis showed that the benefit resulted from a decrease in omega-6 fatty acid and increased omega-3s.

"Where's the meat?"- or should I say, "the fish," because the essential arbiter of in vitro studies and theory is the clinical trial.

Chan et al. (Cancer Causes Control, Mar 2006), "Diet after diagnosis and the risk of prostate cancer progression, recurrence and death," reported a retrospective study showing that among 392 men with localized/regional cancer two servings per week of fish delayed progression by 17%.

Fradet (Clinical Cancer Research, Apr 2009) describes that omega-3s reduce inflammation "and in turn may decrease risk of prostate cancer and progression". This study of 466 men found that an increased intake of omega-3s "was strongly associated with a decreased risk of aggressive prostate cancer".

"A 22-yr prospective study of fish intake in relation to prostate cancer incidence and mortality" (Am J Clin Nutr Nov 2008) followed 2161 men in the Physician's Health Study diagnosed with prostate cancer. Survival analysis revealed "that those consuming fish >or=5 time/wk had a 48% lower risk of prostate cancer death than did men consuming fish less that once weekly".

BOTTOM LINE: The evidence is holding strong that a diet high in omega-3 fatty acids is beneficial to men at all phases of prostate cancer. One can hardly go wrong eating two or three servings of salmon or tuna each week.

BONE METASTSSES AND IMAGING: BONE SCANNING: "When to Perform Bone Scan in Patients with Newly Diagnosed Prostate Cancer: External Validation of the Currently Available Guidelines and Proposal of a Novel Risk Stratification Tool."

The venerable technetium Tc-99m scan is the subject of this review by Briganti et al, EUROPEAN UROLOGY, 2009. This technique remains informative and frequently used, although in many institutions it is being supplanted by the more accurate 18F-labeled sodium fluoride PET (or PET/CT) scan.

As a result of the stage migration that followed the widespread use of PSA screening, clinicians already order staging bone scans more sparingly - and with greater discrimination. The Briganti findings will support clinicians' decisions to customize the utilization of staging bone scans.

The authors employed the Tc-99m in staging 853 consecutive patients to determine the clinical characteristics that best predicted the prevalence of positive scans in specific risk groups categorized by PSA, biopsy Gleason score, and clinical stage. They analyzed the efficiency of detection in their risk groupings in comparison with the guidelines of the AUA, European Association of Urology, NCCN, and the American Joint Committee on Cancer and found that their formulation was the most accurate.

In their study, the accuracy of a positive or equivocal bone scan was reevaluated by CT and/or MRI to confirm the scintigraphy findings. The results were that:

1. In the lowest risk cohort, i.e. Gleason score ≤7, clinical stage T1c, PSA <10 ng/ml, the "rate of bone metastases was virtually null" - 0.2% (1 of 534).
2. In the upper tier of the low-risk group, i.e. Gleason score ≤7, clinical stage T2 or T3, PSA <10 ng/ml, 1.3% had bone metastases (2/158).
3. In the intermediate-risk patients with Gleason score ≤7, clinical stage T2 or T3, PSA >10 ng/ml 8.3% (7/72) of scans were positive; and for the high-risk group: Gleason score 8-10, any PSA, and any clinical stage 16.9% (15/89) showed evidence of bone metastases.

The authors concluded that adherence to their guidelines yielded a "negative predictive value as high as 99.6%", and offered the potential of avoiding many unnecessary staging bone scans.

ADVANCES IN TECHNOLOGY have created several special niches in skeletal staging in prostate cancer. In the JCO report, August 2007, "Magnetic Resonance Imaging of the Axial Skeleton for Detecting Bone Metastases in Patients with High-Risk Prostate Cancer", the authors found that magnetic imaging was superior in both sensitivity and specificity than the Tc-99m scan alone or when supplemented by targeted x-rays. The potential liability of viewing *only* the axial skeleton is offset by studies showing that appendicular skeletal metastases rarely - not never, but rarely - occur without axial components, since the preferred initial pathway of spread from the pelvis is upward via the venous plexus of the axial spine.

Other radiologists, however, argue that the MRI should be reserved for targeted evaluation of equivocal lesions seen on Tc-99 scans.

Many studies are currently evaluating the comparative usefulness of whole-body skeletal MRI scanning compared to scintigraphy.

"SKELETAL PET WITH 18-FLUORIDE: Applying New Technology to an Old Tracer"

reviews the performance of this bone scanning modality. This report by Grant et al. from Harvard and the University of Pennsylvania (Journal of Nuclear Medicine, January 2008, reports comparative studies demonstrating that 18F-fluoride PET has a higher diagnostic accuracy than planar 99m-Tc scans for identifying both malignant and benign lesions of the skeleton.

The 18F-fluoride PET is also recommended by its clinical utility. "The total examination time is approximately 1 h for 18F-fluoride PET, compared with approximately 4 h for 99mTc-MDP bone scintigraphy."

BOTTOM LINE: Validated guidelines are available to assist clinicians in selectively employing bone imaging in the staging of newly diagnosed patients with prostate cancer; and newer technologies are providing improvement in diagnostic accuracy.