Hot SHEET
Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

INSIDE

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New Tool to Determine the Risk of Prostate Cancer Death

Researchers at the University of Copenhagen have identified a new prognostic biomarker: the neuropeptide pro-NPY, which may help determine the risk of dying from prostate cancer. This particular type of protein is very specific to prostate cancer cells and could help identify whether newly diagnosed patients require radical prostatectomy surgery or if it is safe to delay surgery.

Using mass spectrometry, the researchers measured concentration changes in thousands of proteins in both normal and tumour tissue from prostate cancer. Compared to normal tissue, they discovered that the prostate tumors exhibit numerous metabolic alterations including exacerbated activity of mitochondria. Among the 9,000 proteins identified, the neuropeptide, pro-NPY, was demonstrated to exhibit high levels in a subgroup of prostate cancer samples. Pro-NPY was analyzed in 750 patients with prostate cancer to show that pro-NPY levels correlate with increased risk of prostate cancer death.

"Our research shows that high pro-NPY levels are very specific to prostate cancer and can serve to predict prostate cancer related death among diagnosed patients who have not received surgical treatment," says Professor Amilcar Flores-Morales from the Department of Veterinary Disease Biology, University of Copenhagen. The research has been published in the journal, *European Urology*.

"So identifying the biomarker pro-NPY could help us identify patients who would benefit from early active treat-

(Continued on page 5)

A Real-World Study of Prostate Cancer Surveillance

Is active surveillance (AS) a trustworthy and viable method to manage prostate cancer in a variety of practice settings – that is, outside the small group of academic centers that have pioneered and proven the approach in North America? The answer appears to be yes – in the short run at least, according to findings from a nine-site cohort study that includes a veterans administration (VA) hospital and a community-based practice. The study was published in the February issue of *The Journal of Urology* (Vol. 95, pp. 313–320, 2016).

"AS is safe and a good initial strategy. About 10% to 15% of men fall off each year and transition to treatment," summarized investigator Daniel Lin, MD, a urologist at the University of Washington and Veterans Affairs Puget Sound Health Care System in Seattle, WA. This VA center is participating in the Canary Prostate AS Study (PASS), the only multicenter study of AS in North America. Other sites include the Eastern Virginia Medical School in Norfolk, VA, which has a higher percentage of black patients than the other eight study sites.

The cohort study involves 905 men with very-low-, low-, and intermediate-risk prostate cancer (according to National Comprehensive Cancer Network [NCCN] definitions) who were enrolled from 2008 to 2013. Although median follow-up is only 28 months, there have been no prostate-cancer-specific deaths in the cohort, and only two men who transitioned to surgery were found to have positive lymph nodes.

Of the 905 participants, 216 (24%) underwent tumor grade

(Continued on page 6)

Long-Term Toxicity a Surprise Finding with Use of Intermittent ADT for Prostate Cancer

In a surprising study result, the use of intermittent androgen-deprivation therapy (iADT) for prostate cancer is not associated with fewer long-term adverse events than continuous ADT (cADT). The outcome was unexpected because it was hypothesized that the intermittent schedule, which gives patients a break from treatment, would be less harmful.

ADT is associated with an array of adverse events, including sexual dysfunction, bone demineralization, cardiovascular disease, metabolic complications, cognitive changes, and diminished quality of life. In this study of men with metastatic disease – the first to look at long-term health issues – there was a significantly increased incidence of ischemic and thrombotic events with iADT.

The finding comes from an exploratory analysis of data from the landmark Southwest Oncology Group randomized trial (S9346), which compared the two schedules of ADT administration in men with metastatic prostate cancer. The primary outcome was overall survival (OS), and the trial failed to demonstrate noninferiority of iADT vs. cADT, as reported at the 2012 Annual Meeting of the American Society of Clinical Oncology. The study was published online December 23 in *JAMA Oncology*.

For their study, Dr. Hershman and colleagues linked 636 men enrolled in the

(Continued on page 6)

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Clinical Outcomes and Survival Following Treatment of Metastatic Castrate-Refractory Prostate Cancer with Docetaxel Alone or with Strontium-89, Zoledronic Acid, or Both – The TRAPEZE Randomized Clinical Trial

James ND, Pirrie SJ, Pope AM, et al

JAMA Oncol 21 January 2016; Epub

Bony metastatic castrate-refractory prostate cancer (CRPC) has a poor prognosis and high morbidity. Zoledronic acid (ZA) is commonly combined with docetaxel in practice but lacks evidence that combining is effective, and strontium-89 (^{89}Sr) is generally used palliatively in patients unfit for chemotherapy. Phase 2 analysis of the TRAPEZE trial confirmed combining the agents was safe and feasible, and the objectives of phase 3 include assessment of the treatments on survival.

Objective: To determine clinical effectiveness and cost-effectiveness of combining docetaxel, ZA, and ^{89}Sr, all having palliative benefits and used in bony metastatic CRPC to control bone symptoms and, for docetaxel, to prolong survival.

Design, Setting, and Participants: The TRAPEZE trial is a 2 × 2 factorial trial comparing docetaxel alone or with ZA, ^{89}Sr, or both. A cohort of 757 participants was recruited between February 2005 and February 2012 from hospitals in the United Kingdom. Overall, 169 participants (45%) had received palliative radiotherapy, and the median (IQR) prostate-specific antigen level was 146 (51-354). Follow-ups were performed for at least 12 months.

Interventions: Up to 10 cycles of docetaxel alone; docetaxel with ZA; docetaxel with a single ^{89}Sr dose after six cycles; or docetaxel with both ZA and ^{89}Sr.

Main Outcomes and Measures: Primary outcomes included clinical progression-free survival (CPFS) (pain progression, skeletal-related events [SREs], or death) and cost-effectiveness. Secondary outcomes included SRE-free interval, pain progression–free interval, total SREs, and overall survival (OS).

Results: Overall, of 757 participants, 349 (46%) completed docetaxel treatment. Median (IQR) age was 68 (63-73) years. Clinical progression-free survival did not reach statistical significance for either ^{89}Sr or ZA. Cox regression analysis adjusted for all stratification variables showed benefit of ^{89}Sr on CPFS (hazard ratio [HR], 0.85; 95% CI, 0.73-0.99; P = .03) and confirmed no effect of ZA (HR, 0.98; 95% CI, 0.85-1.14; P = .81); ZA had a significant effect on SRE-free interval (HR, 0.78; 95% CI, 0.65-0.95; P = .01). For OS, there was no effect of either ^{89}Sr (HR, 0.92; 95% CI, 0.79-1.08; P = 0.34) or ZA (HR, 0.99; 95% CI, 0.84-1.16; P = 0.91).

Conclusions and Relevance: Strontium-89 combined with docetaxel improved CPFS but did not improve OS, SRE-free interval, or total SREs; ZA did not improve CPFS or OS but did significantly improve median SRE-free interval and reduced total SREs by around one-third, suggesting a role as post-chemotherapy maintenance therapy.

Flip Flop: ED Drugs Not Tied to Prostate Cancer Return

One year ago, German researchers published a single-center study of 4,752 men with prostate cancer that showed an association between the use of erectile dysfunction (ED) drugs (after radical prostatectomy [RP]) and biochemical recurrence (BCR). The drugs, known as phosphodiesterase type 5 inhibitors (PDE5i), are a first-line treatment for the ED that commonly occurs after RP.

"The study made quite a splash," said Stacy Loeb, MD, a urologist at New York University in New York City, who was not involved with the German research. She told Medscape that some clinicians had a subsequent "hesitation" to use these drugs because of "concern that the finding was real."

Last year, the German researchers said they were "astonished" by the link between the use of a PDE5i and BCR after RP. They had theorized that the ED drugs would be protective. In their new study, Dr. Loeb and a team of international researchers decided to take another look at the issue. But they used bigger, more authoritative data sources from Sweden: the nationwide population-based National Prostate Cancer Register, and the Prescribed Drug Register.

Of the men with localized prostate cancer who underwent primary RP or radiation therapy (RT) in 2006 or 2007 and who had five years of follow-up, the investigators identified 293 with BCR after treatment and 5,767 control subjects without BCR. PDE5i pills were used after treatment by 150 (51%) men in the BCR group and 3,334 (58%) in the control group. Pills includ-

(Continued on page 4)

The Role of Targeted Prophylactic Antimicrobial Therapy before Transrectal Ultrasonography-Guided Prostate Biopsy in Reducing Infection Rates: A Systematic Review

Cussans A, Somani BK, Basarab A, Dudderidge TJ

BJU Int 2 February 2016; Epub

To compare the incidence of infective complications after transrectal ultrasonography (TRUS)-guided biopsy with empirical fluoroquinolone (FQ) or culture-based targeted antimicrobial prophylaxis, and the prevalence of FQ resistance (FQ-R) in men undergoing prostate biopsy. A systematic review of the literature was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included studies of men undergoing TRUS-guided biopsy that compared infective outcomes of those who received targeted antimicrobial therapy based on the results of pre-procedural rectal swab cultures, with those receiving empiric FQ prophylaxis. The prevalence of FQ-R was recorded as a secondary outcome measure. Studies with no control group were excluded. Of 125 studies screened, nine studies (4,571 men) met the inclusion criteria. All studies were of cohort design, and included a combination of retrospective and prospective data. Six were undertaken in North America. The remaining studies were undertaken in Spain, Turkey and Columbia. Within these studies, 2,484 (54.3%) men received empirical FQ prophylaxis, whilst 2,087 (45.7%) had pre-biopsy rectal swabs and targeted antibiotics. The mean FQ-R was 22.8%. Post-biopsy infection and sepsis rates were significantly higher in groups given empirical FQ prophylaxis (4.55% and 2.21%) compared with groups receiving targeted antibiotics (0.72% and 0.48%). Based on these results 27 men would need to receive targeted antibiotics to prevent one infective complication. Our systematic review suggests that targeted prophylactic antimicrobial therapy before TRUS-guided prostate biopsy is associated with lower rates of sepsis. We therefore recommend changing current pathways to adopt this measure.

Doc Moyad's What Works & What is Worthless Column, Also Known As "No Bogus Science" Column

"www.cvriskcalculator.com – do this now or else you will be in deep Hot Sheet!"

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor's Note: Us TOO invites certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Aspirin continues to look like a potential anti-prostate cancer agent, or it might help to prevent prostate cancer from coming back after treatment. (Gee who has been saying this for over a decade? Sarcasm alert!). However, if you are otherwise healthy, only take aspirin after a VERY CAREFUL ANALYSIS THAT THE BENEFITS EXCEED THE RISKS. One of the best ways to figure this out working with your doctor is to now go to www.cvriskcalculator.com.

Remember the last issue of the Us TOO *Hot SHEET*? Of course you do! On the cover was why Brad Pitt might be leaving his wife and why Tom Brady's wife no longer wants to be with him, and what the Kardashian family had for breakfast?! What? Wait a second! This was a different cover of a different thing in my mail, and not the *Hot SHEET*. Although, you have to admit that the title "*Hot SHEET*" sounds like either a swear word combined with the word "Hot" (think of the word "ship" but replace the "p" with a "t") or it also sounds like a tabloid oncology newsletter title that will reveal the latest scandals and affairs! Man that would be fun but simultaneously boring to read. "Prostate cancer researcher gets a divorce and dates 23 year old, or prostate cancer clinician arrested for smoking pot outside of Colorado…." Ahh think of the possibilities Tom Kirk and Us TOO – you could make a fortune!

I digressed for a moment, and in reality the cover of the last issue of the *Hot SHEET* was about the new impressive research on aspirin as a potential way of reducing cancer recurrence (not definitive proof but one of the longest studies ever to look at this issue) or reducing the risk of lethal prostate cancer! I will not review this data again but as important as any positive aspirin article you will ever see it must be kept in mind that whether or not the benefits of taking aspirin (reduces heart attacks, stroke, colon cancer, maybe prostate cancer progression) outweigh the negative (ulcers, internal bleeding, need for transfusion, kidney damage).

So, everyone reading this column, and I mean everyone, has to go to the new and arguably best questionnaire and calculator ever invented to help you determine if you might need an aspirin and/or statin if you are otherwise healthy (it assumes you have not had a heart attack or stroke). I tell prostate cancer patients to go to this website everyday and calculate their 10-year risk of heart disease or stroke: www.cvriskcalculator.com. It takes seconds. Then discuss it with your doctor to see if the benefits of taking aspirin and/or a statin outweigh the negative (calculator is for men and women). The site asks you to enter the following: age, gender, race, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, whether you are being treated for high blood pressure, whether or not you have diabetes, and smoking status and that is all! DONE!!! For example, the site says that I (Mark Moyad) would not qualify for an aspirin or statin, but in the future I might (the higher the percentage risk the greater the chance you qualify). Regardless, this is the first step toward figuring out if you need aspirin after being treated for prostate cancer because you want to base this decision on your cardiovascular risk (so you can get a two-for-one so to speak). Finally, I do wish the *Hot SHEET* was a tabloid oncology monthly newsletter because I can see my name in lights now: "Moyad Caught Giving a Hug to an Ohio State Fan while Intoxicated at a Columbus, Ohio Bar." Or "Tom Kirk Skips Cancer Meeting to Vacation in Michigan!" Or, "Us TOO Member Caught Drinking Light Beer Over Regular Beer!" Oh this stuff would be juicy man, really juicy!

Efficacy and Safety of Enzalutamide Versus Bicalutamide for Patients with Metastatic Prostate Cancer (TERRAIN): A Randomized, Double-Blind, Phase 2 Study

Shore ND, Chowdhury S, Villers A, et al

Lancet Oncology 2016; 17: 153–163

Background: Enzalutamide (ENZ) is an oral androgen-receptor inhibitor that was shown to improve survival in two placebo-controlled phase 3 trials, and is approved for men with metastatic castration-resistant prostate cancer (mCRPC). The objective of the TERRAIN study was to compare the efficacy and safety of ENZ with bicalutamide (CAS) in men with mCRPC.

Methods: TERRAIN was a double-blind, randomised phase 2 study, that recruited asymptomatic or minimally symptomatic men with prostate cancer progression on androgen-deprivation therapy (ADT) from academic, community, and private healthcare provision sites across North America and Europe. Eligible men were randomly assigned (1:1) via an interactive voice response system to receive ENZ 160 mg/day or CAS 50 mg/day, both taken orally, in addition to ADT, until disease progression. Men were stratified by a permutated block method (block size of four), by whether bilateral orchiectomy or receipt of luteinizing hormone-releasing hormone agonist; or antagonist therapy started before or after the diagnosis of metastases, and by study site. Patients, investigators, and those assessing outcomes were masked to group assignment. The primary endpoint was progression-free survival (PFS), analyzed in all randomized patients. Safety outcomes were analyzed in all men who received at least one dose of study drug. The open-label period of the trial is in progress, wherein men still on treatment at the end of the double-blind treatment period were offered open-label ENZ at the discretion of the patient and study investigator.

Findings: Between March 22, 2011, and July 11, 2013, 375 men were randomly assigned, 184 (49%) to ENZ and 191 (51%) to CAS; 126/184 (68%) and 168/191 (88%) men, respectively, discontinued their assigned treatment before study end, mainly due to progressive disease. Median follow-up was 20.0 months (IQR 15.0–25.6) in the ENZ group and 16.7 months (10.2–21.9) in the CAS group. Men in the ENZ group had significantly improved median PFS (15.7 months [95% CI 11.5–19.4]) vs. men in the CAS group (5.8 months [4.8–8.1]; hazard ratio 0.44 [95% CI 0.34–0.57]; p <0.0001). Common adverse events occurring with ENZ and CAS, respectively were fatigue (28% vs. 20%), back pain (19% vs. 18%), hot flushes (15% vs. 11%), nausea (17% vs. 14%), constipation (13% vs. 13%), and arthralgia (16% vs. 10%). Common grade 3 or worse adverse events in the ENZ and CAS treatment groups, respectively, were hypertension (7% vs. 4%), hydronephrosis (2% vs. 4%), back pain (3% vs. 2%), pathological fracture (3% vs. 1%), shortness of breath (2% vs. 1%), bone pain (1% vs. 2%), congestive heart failure (2% vs. 1%), heart attack (3% vs. 0%), and anemia (2% vs. 0%). Serious adverse events were reported by 57/183 (31%) men and 44/189 (23%) men in the ENZ and CAS groups, respectively. One of the nine deaths in the ENZ group was thought to be possibly related to treatment (due to systemic inflammatory response syndrome) compared with none of the three deaths in the CAS group.

The data from the TERRAIN trial support the use of ENZ rather than CAS in men with asymptomatic or mildly symptomatic mCRPC.

ED Drugs Not Tied to Prostate Cancer Recurrence *(Continued from page 2)*

ed sildenafil , vardenafil, and tadalafil.

"We found no significant relationship between PDE5i use with prostate cancer recurrence after treatment," Dr. Loeb and her colleagues conclude in their study, which was published online 30 December 2015 in the journal *European Urology*.

"The paper from Germany hasn't been validated," Dr. Loeb satated. "Thankfully, it hasn't panned out. The take-home message is not to worry about this."

One of the authors of the German study agrees, for the most part. "The now-published evidence... suggests that the use of erectile drugs – which are unfortunately often necessary after RP – do not harm the patient," said Thorsten Schlomm, MD, from the Martini-Clinic Prostate Cancer Center at the University Medical Center Hamburg–Eppendorf in Germany. The evidence includes another recent single-center study (from Italy), which, like the Swedish study, did not find a tie between ED drugs and cancer recurrence (Eur Urol, Vol. 68, pp. 750–753).

However, Dr. Schlomm, who was also an investigator on the Swedish study, defended the German study, which was conducted at the Martini-Clinic – one of the biggest prostate cancer clinics in the world. "We believe that the differences between our initial data are mainly based on the different patient cohorts," he stated. In the German study, which only included men who underwent surgery, the majority of patients had an organ-defined disease.

"We believe that a small biological effect (for example, from PDE5i) can be more likely detected in men with a more favorable overall prognosis than in men with a more aggressive tumor," Dr. Schlomm explained. In the Sweden study, the mix of patients was more heterogeneous, he pointed out. Nevertheless, Dr. Schlomm called the new results "good news."

Specifically, the Swedish study showed that PDE5i use was not associated with BCR after RP (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.59–1.03) or RT (OR, 0.98; 95% CI, 0.49–1.97), after adjustment for a wide variety of potential confounders, including marital status, income, and Gleason score. Results were similar after additional adjustment for surgical pathology (OR, 0.86; 95% CI, 0.64–1.16).

The Swedish study results suggest that ED drugs might even be protective. Men whose cumulative number of PDE5i pills was above the median had a slightly lower risk for BCR after RP in the clinical model, and there was no difference in the risk for BCR after adjustment for pathologic tumor features.

Medscape Medical News
2 February 2016

Use of Two Gene Panels for Prostate Cancer Diagnosis and Patient Risk Stratification

Xiao K, Guo J, Zhang X, et al

Tumour Biol 28JAN16; Epub

Currently, no ideal prostate cancer (PCa) diagnostic or prognostic test is available due to a lack of biomarkers with high sensitivity and specificity. There is an unmet medical need to develop combinations of multiple biomarkers which may have higher accuracy in detection of PCa and stratification of aggressive and indolent cancer patients.

The aim of this study was to test two biomarker gene panels in distinguishing PCa from benign prostate and high-risk, aggressive PCa from low-risk, indolent PCa, respectively. We identified a five-gene panel that can be used to distinguish PCa from benign prostate. The messenger RNA (mRNA) expression signature of the five genes was determined in 144 PCa and benign prostate specimens from radical prostatectomy (RP). We showed that the five-gene panel distinguished PCa from benign prostate with sensitivity of 96.6%, specificity of 92.9%, and area under the curve (AUC) of 0.992 (p <0.0001). The five-gene panel was further validated in a 137 specimen cohort and showed sensitivity of 84.6%, specificity of 91.84%, and AUC of 0.942 (p <0.0001). To define subtypes of PCa for treatment guidance, we examined mRNA expression signature of an eight-gene panel in 87 PCa specimens from RP. The signature of the eight-gene panel was able to distinguish aggressive PCa (Gleason score >6) from indolent PCa (Gleason score ≤6) with sensitivity of 90.3%, specificity of 80.0%, and AUC of 0.967 (p <0.0001). This panel was further validated in a 158 specimen cohort and showed significant difference between aggressive PCa and indolent PCa with sensitivity of 92.6%, specificity of 70.0 %, and AUC of 0.962 (p <0.0001). Our findings in assessing multiple biomarkers in combination may provide new tools to detect PCa and distinguish aggressive and indolent PCa for precision and personalized treatment. The two biomarker panels may be used in clinical settings for accurate PCa diagnosis and patient risk stratification for biomarker-guided treatment.

Prospective Study Evaluating $Na^{18}F$-Positron Emission Tomography/ Computed Tomography (NaF-PET/CT) in Predicting Clinical Outcomes and Survival in Advanced Prostate Cancer

Apolo AB, Lindenberg L, Shih JH, et al

J Nuclear Med 21 January 2016, Epub

This prospective pilot study evaluated the ability of sodium fluoride ($Na^{18}F$) positron emission tomography/ computed tomography (NaF-PET/CT) to detect and monitor bone metastases over time and its correlation with clinical outcomes and survival in advanced prostate cancer.

Patients and Methods: Sixty prostate cancer patients, including 30 with and 30 without known bone metastases by conventional imaging underwent NaF-PET/CT at baseline, six, and 12 months. Positive lesions were verified on follow-up scans. Changes in standardized uptake values (SUV) and lesion number were correlated with prostate-specific antigen (PSA) change, clinical impression, and overall survival (OS).

Results: Sixty patients underwent 170 NaF-PET/CT scans. Significant associations included SUV and PSA percent change at 6 (P = 0.014) and 12 months (P = 0.0005); SUV maximal percent change from baseline and clinical impression at six months (P = 0.0147) and six-12 months (P = 0.0053); SUV change at six months and OS (P = 0.018); number of lesions on NaF-PET/CT and clinical impression at baseline (P <0.0001), six (P = 0.0078), and 12 months (P = 0.0029); number of lesions on NaF-PET/CT per patient at baseline and OS (P = 0.017). In an exploratory analysis, paired (^{99}m)Tc-MDP bone scans (TcBS) were available in 35 patients at baseline, 19 at six months, and 14 at 12 months (n = 68 scans). Malignant lesions on NaF-PET/CT (n =57) were classified on TcBS as malignant 65%; indeterminate 25%; and negative 10%. Additionally 65% of paired scans showed more lesions on NaF-PET/CT than on TcBS.

Conclusions: Baseline number of malignant lesions and changes in SUV on follow-up NaF-PET/CT significantly correlates with clinical impression and OS. NaF-PET/CT detects more bone metastases earlier than TcBS and enhances detection of new bone disease in high-risk patients.

Pro-NPY

(Continued from page 1)

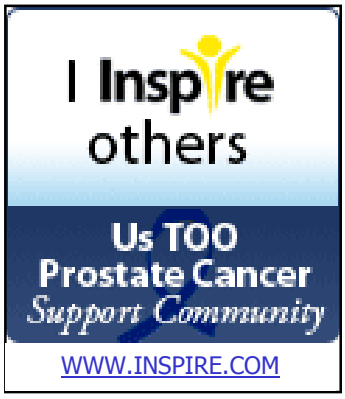
ment, whereby we would also reduce unnecessary treatment of patients who undergo surgery when they have low-grade tumors that for the most part do not put their lives at risk. In the end, due to side effects, this could prove more harmful than beneficial to patients," adds Amilcar Flores-Morales.

Proteins are key effectors of cellular functions. Therefore, a better understanding of the protein signaling pathways deregulated in prostate cancer could lead to better preventive and therapeutic strategies for the treatment of this disease. Specifically, it is possible that metabolic alterations such as the increase in mitochondria activity could be targeted in the treatment of prostate cancer.

"We hope to contribute to the advance of translational cancer research and the implementation of precision medicine in the field of prostate cancer by providing a unique insight into the protein level alterations associated with tumor tissue in clinical samples," added Flores-Morales.

This work is the result of collaborations between research groups of Professor Flores-Morales at IVS, Professor

(Continued on page 8)



Real-World Study of AS *(Continued from page 1)*

and/or volume reclassification, which was the primary study end point. Men were "reclassified" on the basis of two measures: increased Gleason grade (primary or sum); and greater tumor volume (a ratio of positive to total number of cores; where a ratio below or above 34% indicatives stability or an increase, respectively). Investigators prefer the term reclassification over progression because undersampling at diagnosis can explain why a more serious prostate cancer is not detected initially.

Notably, many men offered treatment did not jump at the opportunity. Of 216 men reclassified , 83 (38%) remained on AS or were considering treatment. Another 115 (53%) underwent definitive treatment and 18 dropped out of PASS without confirmed treatment. Of the 689 men who did not undergo disease reclassification, 560 remained on AS, 55 opted for treatment, and 74 dropped out.

"The dropout rate in the Canary PASS study appears to be higher than at least one of the pioneering centers. Only 2.5% of men in the Sunnybrook (Toronto) cohort have been lost to follow-up," principal investigator Lawrence Klotz, MD said in 2014. In the Canary PASS study, the probability of a man remaining on AS two years after diagnosis was 88%; five and 10 years post-diagnosis, 71% and 50% of men remained on AS, respectively, according to Kaplan–Meier estimates.

Overall, of the men who underwent RP after a period of AS, 34 (33%) were pathologically upgraded at RP and 14 (14%) were downgraded. A total of 35 men (34%) had adverse pathologic features at RP, including a primary Gleason pattern of 4 or 5, extraprostatic extension, seminal vesicle invasion, or lymph node metastasis.

"This is real-world AS. It's very important to have this dataset," said Alexander Kutikov, MD, a urologist from the Fox Chase Cancer Center in Philadelphia, PA, who was asked for comment and was not involved with the research. He pointed out that a majority of the Canary PASS sites are major academic cancer centers.

Investigators emphasized, "Importantly, there was no significant relationship between risk classification (very low, low, and intermediate) at diagnosis and adverse pathology at surgery."

Specifically, the percentage of men who, after a period of being watched, had adverse pathology at RP was similar in the three risk categories; 37% were classified as very-low risk at diagnosis, 32% as low-risk, and 40% as intermediate- or high-risk. This finding was the biggest "takeaway" for Dr. Kutikov. "NCCN risk stratification didn't really correlate with adverse pathology [at RP]," he said. "In this study, it didn't matter what your risk group was."

The clinical factors associated with reclassification were "weak" or "modest," Dr. Lin pointed out. "Clinical factors cannot adequately predict who will progress," he said. However, the study did show that PSA density, tumor volume, and body mass index "do seem to have a modest association with grade progression."

"A more biologically based assessment of risk at diagnosis, as well as during periodic re-evaluation, is needed," Dr. Lin said. "It's up to us to find better markers," he added.

Medscape Medical News
22 January 2016

More Toxicity Seen with iADT *(Continued from page 1)*

S9346 trial who had no private insurance with their Medicare claims to investigate differences in long-term adverse events. The adverse events were grouped into five categories: endocrine events, sexual dysfunction, dementia and depression, acute kidney injury, and ischemia and thrombosis.

For the first four categories, there was no significant difference between groups. But the 10-year cumulative incidence of ischemic and thrombotic events differed significantly; it was 24% in the cADT group and 33% in the iADT group (hazard ratio, 0.69; P = 0.02).

The men had a median age of 71 years and overall, had a lot of health issues. "The reality is that long-term, health-related events were high in both arms," said Dr. Hershman. The most common long-term events were hypercholesterolemia (31%) and osteoporosis (19%).

Dr. Hershman also observed that all of the men in the study received ADT prior to randomization. "Therefore, the benefits of iADT on chronic complications may be limited," she said, explaining the unexpected results.

A pair of Canadian experts, Saroj Niraula, MBBS, MD, from the University of Manitoba in Winnipeg, and Ian F. Tannock, MD, PhD, from the University of Toronto, wrote an accompanying editorial. The findings are weakened by "methodological limitations," they stated. "Neither the primary SWOG study nor the current one was powered adequately to examine differences in occurrence of toxic effects between the two strategies. Thus, the study does not prove the statistical superiority of cADT in terms of thromboembolic and ischemic events. However, the pair acknowledged that, given the direction of this trend, "it is highly unlikely that a larger RCT would find [the events] to be reduced with iADT."

Editorialists and the study authors speculate as to why there were more ischemic and thrombotic events with iADT. The authors call the result "counterintuitive."

Among other thoughts, the editorialists said: "Multiple insults to the coagulation system with decrease and increase in testosterone levels during iADT might therefore be responsible for the observations in the study."

The authors touch on that same idea: "Changes in the coagulation cascade have been reported with lowering of testosterone during ADT as well as with increasing estrogen (after stopping ADT)."

The authors conclude that iADT is something that clinicians should be "cautious" about using in elderly men with metastatic prostate cancer. They added that more study is needed in this area.

But the editorialists provide a slightly different summary, which accents the positive.

Any advantage of iADT is likely to be limited to possible improvements in QOL particularly during the off-treatment period; convenience of therapy; and savings in cost.

Medscape Medical News
6 January 2016

Affected by Prostate Cancer?
Us TOO
SUPPORT - EDUCATION - ADVOCACY

Doctor Chodak's Bottom Line *(Page number and first few words of article title)*

Gerald Chodak, MD, Author, *Winning the Battle Against Prostate Cancer*, Second Edition http://www.prostatevideos.com/

Editor's Note: Us TOO has invited certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

P1, "Real-life Study" – More information is beginning to appear about outcomes following active surveillance (AS) and the results are somewhat mixed. Lin and co workers reported their early results from several non-academic medical centers. With a median follow-up of less than three years, no one has died from prostate cancer. However, 24% were reclassified either because of increased tumor grade or tumor volume. As has been seen in other reports, many men decide not to follow the recommendation to either stay on AS or proceed to definitive treatment. So longer follow-up of those that choose to remain on AS is important. Also, better criteria are needed for deciding when men should stop AS and receive definitive therapy because one-third of those undergoing surgery had adverse pathologic features. This rate was similar for men initially diagnosed with very-low, low-, and intermediate-risk disease. Importantly, that represents less than 4% of the entire group. Their long-term outcome will help men fully understand the risk from this approach.

The Bottom Line: Early data from men on AS from non-academic centers is showing that men who progress and are treated by radical prostatectomy have about a 4% chance of adverse pathology.

P1, "New Tool" – Ultimately, doctors would love to have a test that could distinguish the most dangerous prostate cancers so they could be offered definitive therapy rather than AS. Researchers from the University of Copenhagen searched for novel proteins that might help identify men at risk of dying from their disease. They found that neuropeptide pro-NPY might be a useful marker for that purpose. More data will be needed on different subsets of men to determine exactly how accurate this test might be and how it compares with other genetic marker tests being used to identify high-risk patients.

The Bottom Line: Pro-NPY may warrant further investigation as a potential marker to identify men at risk of dying from prostate cancer.

P1, "Long-term Toxicity" – Considerable debate has occurred over the role of intermittent androgen deprivation therapy (iADT) in men with advanced disease. A randomized study found that it was inferior to continuous therapy for men with metastases but overall survival was similar in men without metastases. Unfortunately, even in the latter study more men on iADT were more likely to die of prostate cancer but less likely to die of other causes, meaning it was still a reasonable option in that group. Now additional data is being presented about the long-term adverse effects. IADT was thought to offer men a better quality of life than continuous therapy. However, the article by Hershmann and co-workers is now reporting that men with metastatic disease on iADT have a significantly higher risk of ischemic and thrombotic events. A similar evaluation is needed for the men with non -metastatic disease.

The Bottom Line: Not only does iADT result in a lower overall survival in men with metastatic disease, it also has a higher risk of adverse effects. This information should be carefully explained to men before they initiate this therapy.

P2, "Clinical Outcomes" – Men with progressive bony metastases prostate cancer face numerous risks as their disease advances. Zoledronic acid and Strontium have been used to reduce some of those risks but their optimal timing has not been well defined. Now results of the TRAPEZE trial have been presented showing that combining zoledronic acid with docetaxel significantly reduced the risk of a skeletal related event (SRE) but had no impact on survival. Combining Strontium with docetaxel provided no significant improvement. Despite these results, an important question is whether denosumab (XGEVA) might be a better treatment to combine with docetaxel; but that will require another randomized study.

The Bottom Line: A combination of zoledronic acid and docetaxel significantly reduces the risk of SREs in men with progressive metastatic prostate cancer to bone.

P2, "Flip Flop" – Beware of non-randomized studies! That has been my recurring message in "The Bottom Line" and it is evident again from the non-randomized German study looking at the long-term effects of erectile dysfunction drugs (ED) given to men following localized treatment of prostate cancer. They reported that men receiving an ED drug had a higher rate of biochemical recurrence compared to men not receiving one of those drugs. Now we have a follow-up study by Loeb and co-workers also from a non-randomized study population and they found no association between those drugs and disease recurrence. Since neither study is randomized we must ask which one is correct? Sadly, we cannot make that determination unless well-designed study is performed. A number of questions would need to be addressed including whether the same result would occur with any of the three ED drugs, how long men received it, the initial and final pathology of the cancer, and whether the same results would occur in men treated with surgery compared to radiation. Until or unless that study is done, it will remain an open question whether ED drugs pose a risk.

The Bottom Line: An open question remains whether ED drugs pose an increased risk of disease recurrence following radical prostatectomy or radiation, but for now, there is no definite evidence that men should refrain from taking those drugs.

P3, "The Role of Targeted" – Among the concerns about screening for prostate cancer is the potential morbidity from infections following a prostate biopsy. Standard practice involves administering an antibiotic prior to the procedure; however, infections still occur due to bacterial resistance. One approach has been to do rectal swabs prior to scheduling the procedure and then tailoring the prophylactic antibiotic accordingly. An analysis of published reports by Cussans et al, found nine studies that met their entry criteria; but unfortunately, it included

(Continued on page 8)

The Bottom Line

(Continued from page 7)

non-randomized study. Regardless, their findings were that targeted antibiotic therapy had a lower incidence of infections compared to using untargeted fluoroquinolones. However, they found that 27 men would need targeted therapy to prevent one infection. That is likely to substantially increase the costs, although a full cost analysis of treating infections that occur without targeted therapy would likely make this approach more cost effective. More data would help to change the standard approach to using routine rectal swabs a targeting the prophylaxis.

The Bottom Line: Rectal swabs and targeted antibiotic therapy appear to offer a more effective approach to preventing infections following prostate biopsy but more data are needed to make it the standard of care.

Even after Antiandrogen Therapy, Docetaxel Remains Useful in Prostate Cancer

A study presented at the 2016 Genitourinary Cancers Symposium (GuS) showed that 40% of patients with metastatic castration-resistant prostate cancer treated with docetaxel following abiraterone (Zytiga®) had at least a 50% reduction in PSA, demonstrating the activity of this drug sequencing. These findings were presented at the Genitourinary Cancers Symposium (GuS) by Thomas W. Flaig, MD, of the University of Colorado Cancer Center, and colleagues.

The multi-institution study followed 1,088 men treated on the clinical trial COU-AA-302. Of those treated with abiraterone, 67% went on to receive further therapies, with 36% receiving two additional therapies and 17% receiving three or more. About half of all abiraterone-treated men on the study were treated with docetaxel in the next line of therapy.

Of the men receiving docetaxel after abiraterone, 40% had PSA decline by more than half, demonstrating the effectiveness of this chemotherapy even after treatment with androgen-deprivation therapy.

"Surprisingly, the next most common 'treatment' after docetaxel in this setting was no treatment at all," Dr. Flaig noted.

"This confirms the activity of abiraterone followed by docetaxel and represents important data on the sequencing of medical therapies under this new paradigm," Dr. Flaig said.

Presented at the 2016 Annual GuS, abstract 168

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20 January 2016

Pro-NPY

(Continued from page 5)

Matthias Mann at Novo Nordisk Foundation Center for Protein Research, both from the Faculty of Health and Medical Sciences together with the Danish Cancer Society Research Center, and Associate Professor Pernilla Wikström from the Umeå University, Sweden. Validation of pro-NPY as a biomarker was made possible by the contribution of patients and clinical researchers from several institutions in Sweden.

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