INSIDE THIS ISSUE

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US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

SEPTEMBER 2013 IS PROSTATE CANCER AWARENESS MONTH

METFORMIN MAY LOWER RISK OF PROSTATE CANCER DEATH, RESEARCHERS SAY

Metformin, a widely used diabetes drug, may reduce the risk of dying from prostate cancer, according to new research. A study of nearly 4,000 diabetic men found that those taking metformin when diagnosed with prostate cancer were less likely to die of the cancer or other causes compared to men using other diabetes drugs.

"We demonstrated that metformin is associated with improved survival among diabetic patients with prostate cancer," said Dr. David Margel, a uro-oncologist at Rabin Medical Center in Petah Tikva, Israel, who conducted the research while at the University of Toronto. "It's associated in a dose-response manner," he said. "The longer you were on metformin, the less likely you were to die of prostate cancer and of all causes."

But whether metformin can prevent prostate cancer progression in people without diabetes remains to be seen, experts say. Type 2 diabetes is rampant, and metformin is the drug most commonly prescribed to treat it. More than 61 million metformin prescriptions were filled in the United States last year. Brand names include Glucophage® and Glumetza®. The drug, in its generic forms and certain brand names, is rela-

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NCI PANEL – STOP CALLING LOW-RISK LESIONS CANCER

The practice of oncology in the United States is in need of a host of reforms and initiatives to mitigate the problem of overdiagnosis and overtreatment of cancer, according to a working group sanctioned by the National Cancer Institute.

Perhaps most dramatically, the group says that a number of premalignant conditions, including ductal carcinoma in situ and high-grade prostatic intraepithelial neoplasia, should no longer be called "cancer." Instead, the conditions should be labeled something more appropriate, such as indolent lesions of epithelial origin (IDLE), the working group suggests. The Viewpoint report was published online July 29 in JAMA.

"Use of the term 'cancer' should be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated," write the 3 people who make up the working group – Laura Esserman, MD, MBA, from the University of California at San Francisco; Ian Thompson, MD, from the University of Texas Health Science Center at San Antonio; and Brian Reid, MD, PhD, from the Fred Hutchinson Cancer Research Center in Seattle.

They make a concrete proposal for change: "A multidisciplinary effort across the pathology, imaging, surgical, advocate, and medical communities could be convened by an independent

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FDA DRUG SAFETY COMMUNICATION: FDA LIMITS USAGE OF NIZORAL (KETOCONAZOLE) ORAL TABLETS DUE TO POTENTIALLY FATAL LIVER INJURY AND RISK OF DRUG INTERACTIONS AND ADRENAL GLAND PROBLEMS

The US Food and Drug Administration (FDA) is taking several actions related to Nizoral® (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems and advising that it can lead to harmful drug interactions with other medications. FDA has approved label changes and added a new Medication Guide to address these safety issues. As a result, Nizoral oral tablets should not be a first-line treatment for any fungal infection. Nizoral should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

The topical formulations of Nizoral have not been associated with liver damage, adrenal problems, or drug interactions. These formulations include creams, shampoos, foams, and gels applied to the skin, unlike the Nizoral tablets, which are taken by mouth.

Nizoral tablets can cause liver injury, which may potentially result in liver

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REPETITIVELY DOSED DOCETAXEL AND ^{153}SAMARIUM-EDTMP AS AN ANTITUMOR STRATEGY FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Autio K, Pandit-Taskar N, Carrasquillo J, et al

Cancer 13 June 2013; Epub

Background: β-emitting bone-seeking radiopharmaceuticals have historically been administered for pain palliation whereas docetaxel prolongs life in patients with metastatic castration-resistant prostate cancer (mCRPC). In combination, these agents simultaneously target the bone stroma and cancer cell to optimize antitumor effects. The toxicity and efficacy when each agent is combined at full, recommended doses, in a repetitive fashion is not well established.

Methods: Patients with progressive mCRPC and ≥3 bone lesions received ^{153}Sm-EDTMP (^{153}samarium ethylene diamine tetramethylene phosphonate) at a dose of 1.0 mCi/kg every 9 weeks and docetaxel at a dose of 75 mg/m^2 every 3 weeks. In the absence of unacceptable toxicity, patients were allowed to continue additional cycles, defined by 9 weeks of treatment, until intolerance or biochemical/radiographic disease progression.

Results: Of the 30 patients treated, approximately 50% were considered to be taxane-naive, 36.7% were taxane-refractory, and 13.3% had previously been exposed to taxanes but were not considered refractory. Patients received on average 2.5 cycles of treatment (6.5 doses of docetaxel and 2.5 doses of ^{153}Sm-EDTMP). Twelve patients (40%) demonstrated a decline in their prostate-specific antigen level of ≥50%. The median progression-free survival (biochemical or radiographic) was 7.0 months and the overall survival was 14.3 months. Nine patients (30%) did not recover platelet counts >100 K/mm^3 after a median of 3 cycles to allow for additional treatment, with 4 patients experiencing prolonged thrombocytopenia. The most common reasons for trial discontinuation were progressive disease and hematologic toxicity.

Conclusions: The results of the current study indicate that ^{153}Sm-EDTMP can be safely combined with docetaxel at full doses on an ongoing basis in patients with mCRPC. Although thrombocytopenia limited therapy for some patients, preliminary efficacy supports the strategy of combining a radiopharmaceutical with chemotherapy, which is an appealing strategy given the anticipated availability of α-emitters that can prolong survival.

DEFINING A NEW TESTOSTERONE THRESHOLD FOR MEDICAL CASTRATION: RESULTS FROM A PROSPECTIVE COHORT SERIES

Dason S, Allard CB, Tong J, Shayegan B

Can Urol Assoc J 7: E263-237, 2013

Background: We seek to determine if testosterone (T) levels below the accepted castration threshold (50 ng/dL) have an impact on time to progression to castrate-resistant prostate cancer (CRPC).

Methods: This is a prospective cohort series of men undergoing androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone agonist or antagonist at a tertiary centre from 2006 to 2011. Serum T level was assessed every 3 months. Men with any T >50 ng/dL were excluded. Men were stratified into groups based on those achieving mean T levels <20 ng/dL and <32 ng/dL. Progression to CRPC was assessed with the Kaplan-Meier method and compared with the log-rank test.

Results: A total of 32 men were included in this study. Mean follow-up was 25.7 months. Men with a 9-month serum T < 32 ng/dL had a significantly increased time to CRPC compared to men with T 32 to 50 ng/dL (p = 0.001, median progression-free survival (PFS) 33.1 months [< 32 ng/dL] vs. 12.5 months [>32 ng/dL]). Men with first year mean T < 32 ng/dL also had a significantly increased time to CRPC compared to 32 to 50 ng/dL (p = 0.05, median PFS 33.1 months [< 32 ng/dL] vs. 12.5 months [32-50 ng/dL]). A T < 20 ng/dL compared to 20 to 50 ng/dL did not significantly predict with time to CRPC.

Conclusion: This study supports a lower T threshold to define optimal medical castration (T <32 ng/dL) than the previously accepted standard of 50 ng/dL. T levels during ADT serve as an early predictor of disease progression and thus should be measured in conjunction with prostate-specific antigen.

ENDURANCE TRAINING IN PROSTATE CANCER PATIENTS TREATED WITH ANDROGEN DEPRIVATION THERAPY

Hvid T, Winding K, Rinnov A, et al

Endocr Relat Cancer, 6 June 2013; Epub

Background: Insulin resistance and changes in body composition are side effects of androgen deprivation therapy (ADT) given to prostate cancer patients. The present study investigates if endurance training improves insulin sensitivity and body composition in ADT-treated prostate cancer patients.

Methods: Nine men undergoing ADT for prostate cancer and 10 healthy men with normal testosterone levels underwent 12 weeks of endurance training. Primary endpoints were insulin sensitivity (euglycemic hyperinsulinemic clamps with concomitant glucose-tracer infusion) and body composition (dual-energy x-ray absorptiometry and magnetic resonance imaging). The secondary endpoint was systemic inflammation.

Statistics: Two-way ANOVA.

Results: Endurance training increased VO_2max (ml(O_2)/min/kg) by 11% and 13% in patients and controls, respectively ($p < 0.0001$). The patients and controls demonstrated an increase in peripheral insulin sensitivity of 14% and 11%, respectively ($p < 0.05$), with no effect on hepatic insulin sensitivity ($p=0.32$). Muscle protein content of GLUT4 and total Akt was also increased in response to the training ($p < 0.05$ and $p < 0.01$, respectively). Body weight ($p < 0.0001$) and whole-body fat mass ($p < 0.01$) were reduced, while lean body mass ($p=0.99$) was unchanged. Additionally, reductions were noted in abdominal ($p < 0.01$), subcutaneous ($p < 0.05$) and visceral fat mass ($p < 0.01$). Plasma markers of systemic inflammation were unchanged in response to the training. No group X time interactions were found, except for thigh intermuscular adipose tissue (IMAT) ($p=0.01$), reflecting a significant reduction in IMAT in controls ($p < 0.05$) not observed in patients ($p=0.64$).

Conclusion: In response to endurance training, ADT-treated prostate cancer patients improved insulin sensitivity and body composition to a similar degree as eugonadal men.

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"Obesity deaths have been underestimated ?"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line: New research suggests that almost 20% of premature deaths are associated with excess body weight, which is about 4 times higher compared to other estimates! Yikes!

Remember in the last issue of US Too *HotSheet* I discussed how there was too much concern with an omega-3 fatty acid or fish oil study, and not enough attention to the fact that in that same study more than 51% of the men were overweight and over 35% of the men were obese in the high-grade prostate cancer group! In other words, while we are all running around and talking about which supplements can help or harm we are ignoring or being distracted away from an epidemic that is really killing many people at an early age.

And, now new research suggests it is responsible for a lot more deaths than we ever imagined in younger and older individuals. The death toll from the US obesity epidemic appears to be 4 times higher than was previously believed. This study was the first to account for differences in age, sex, and race, and birth cohort. Right now about one third of Americans are obese which is roughly 35 pounds heavier than a healthy weight. Obesity increases the risk for cardiovascular disease, type-2 diabetes, many cancers and other diseases.

Part of the problem of previous published estimates is due to the fact that many more diseases are associated with obesity among older adults and the higher rates of obesity among younger generations. It is possible that this new estimate is a little off, but I agree with it for the most part statistically because every passing year research finds another disease or situation that increases with obesity. For example, aggressive prostate cancer is now more closely linked to obesity compared to the past when research was not certain.

Basically, my point is this – the next time you get distracted by an article on which drug or supplement to take in the future please ask yourself if you are doing everything possible to reduce your risk of abnormal weight gain, which is another way of saying are you looking at the forest over the trees. I have had countless men and women ask me about that omega-3 study and prostate cancer in the past month and in almost every case the person asking me was struggling with a serious weight problem. And, this does make sense because weight loss is so darn hard and difficult and it takes most or all of your attention to combat this problem, which is why focusing on other health concerns such as fish oil right now has to be one of the greatest distractions of the year. It is kind of like knowing your house is on fire and before you call 911 you want to know if you need to fix a small leak in the roof. Every second counts so putting out the fire needs your complete attention. When that has been taken care of, we can then talk about the leaky roof. Unfortunately, many of us, including health care professionals have become obsessed with leaky roofs during house fires!

Okay, this is Bob Vila signing off now but I think you get my point!

<u>Reference</u>:

1. Masters RK, Reither EN, Powers DA, et al. The impact of obesity on us mortality levels... Am J Pub Health, posted online 15 August 2013.

GAO TARGETS SELF REFERRALS FOR RADIATION THERAPY

A government watchdog agency is once again calling into question self-referring physicians – this time for prostate cancer (PCa) radiation therapy (RT) – during the same week lawmakers filed a bill to ban the practice.

Use of the pricey intensity-modulated radiation therapy (IMRT) to treat PCa nearly doubled among physicians who began to self-refer from 2006 to 2010, while increasing modestly in groups that don't self-refer, said the Government Accountability Office (GAO). Physicians who began self-referring during the time frame studied increased referrals for IMRT by 46.6%, while those who were already self-referring dropped by 5.1%, they found. Those who didn't self-refer increased their use of IMRT by 5.5% from 2006 to 2010.

"Taken together, our findings suggest that financial incentives were likely a major factor driving the increase of IMRT referrals among self-referring providers in limited-specialty groups," the GAO stated.

Also, Representatives Jim McDermott, MD (D-WA) and Jackie Speier (D-CA) introduced a bill – the Promoting Integrity in Medicare Act (H.R. 2914) – that would ban self-referral for advanced imaging, anatomic pathology, RT, and physical therapy services.

In the GAO report, Congress called IMRT one of the most costly options for PCa, consuming more than half of the $1.27 billion Medicare paid for PCa treatment in 2010. However, treatment choices for low-risk PCa (e.g., IMRT, brachytherapy, hormone therapy, and radical prostatectomy) depend on a number of factors, including health status, life expectancy, personal choice, and provider recommendations.

The American Association of Clinical Urologists, American Urological Association, and the Large Urology Group Practice Association denounced the GAO report. The groups said the GAO ignored peer-reviewed literature that states IMRT has become the standard of care for PCa. Furthermore, the agency didn't recommend stopping the self-referral practice.

Senate Finance Committee Chair Max Baucus (D-MT) along with Sen. Chuck Grassley (R-IA), Rep. Sander Levin (D-MI), and Rep. Henry Waxman (D-CA) requested the GAO report.

"When you look at the numbers in this report, you start to wonder where healthcare stops and where profiteering begins," Baucus stated. "We have a law on the books designed to prevent these conflicts of interest, but an increasing number of physicians are skirting the law for their own personal gain. Enough is enough. Congress needs to close this loophole and fix the problem."

Baucus was referring to the Stark Law prohibiting physicians from making referrals to facilities in which they have a financial relationship – except for certain in-office ancillary care like diagnostic and therapeutic services. Lawmakers introducing the self-referral bill Thursday pointed to the Stark Law's exceptions as a reason for some unnecessary Medicare spending. "Patient convenience and streamlined services are important, but improper use of the exception creates unneeded costs," McDermott stated. "This legislation will preserve the exception but narrow it to better reflect congressional intent in the Self-Referral law."

The Stark Law aimed to prevent use of services or higher-priced treatments that have little patient benefit but financially benefit physicians, at a higher cost to Medicare. But this third report from GAO in recent months spotlights the issue of higher utilization of more expensive services by self-referring physicians. Previous reports have spotlighted anatomic pathology services and MRIs and CTs. A fourth report on physical therapy services is expected later this year.

The American Society for Radiation Oncology (ASTRO) and other groups, including the American College of Radiology and the American Society for Clinical Pathology, support the bill from McDermott and Speier.

"Closing the self-referral loophole will help stabilize the fee-for-service system today, while we charge ahead on the long, challenging path to developing a fair, high-functioning payment system," stated ASTRO Chairman Michael Steinberg, MD.

MedPage Today, 2 August 2013

LOW-RISK LESIONS

(Continued from page 1)

group (e.g., the Institute of Medicine) to revise the taxonomy of lesions now called cancer and to create reclassification criteria for IDLE conditions."

This change of cancer terminology to reflect validated diagnostic tests that can identify indolent and low-risk lesions is 1 of 5 major reforms proposed by the working group. The scope of these initiatives ranges from cancer screening to cancer prevention.

The reforms are needed because, over the past 30 years or so, cancer screening in the United States has become highly problematic, the group explains.

At the heart of the problem is the fact that programs designed to reduce the rate of late-stage disease and decrease cancer mortality have not met these goals, according to the working group.

Instead, "national data demonstrate significant increases in early-stage disease, without a proportional decline in later-stage disease," they write.

Overdiagnosis occurs "when tumors are detected that, if unattended, would not become clinically apparent or cause death." If not recognized, overdiagnosis "generally leads to overtreatment," notes the working group.

Their Viewpoint mirrors, in a number of major ways, a 2009 essay by Drs. Esserman and Thompson that called for a "rethinking" of prostate and breast cancer screening, in part because of the overtreatment of indolent and low-risk lesions. That essay prompted the chief medical officer of the American Cancer Society to famously declare, in an interview with a major news outlet, that "the advantages to screening have been exaggerated," which triggered a firestorm of controversy.

The working group hopes "that altering the semantics will reduce the anxiety brought about by one of these diagnoses," Dr. Sekeres stated. However, substituting the word cancer with other terms is a "bit of a workaround," he noted. "What doctors should really be doing is communicating more effectively with their patients, and putting into context whatever finding they have."

Medscape Medical News, 30 July 2013

KETOCONAZOLE WARNING

(Continued from page 1)

transplantation or death. FDA has revised the Boxed Warning, added a strong contraindication in patients with liver disease, and included new recommendations for assessing and monitoring patients for liver toxicity.

Serious liver damage has occurred in patients receiving high doses of Nizoral for short intervals as well as those receiving low doses for long periods. Some of these patients had no obvious risk factors for liver disease. The liver injury is sometimes reversible upon stopping the drug, but that is not always possible.

Nizoral tablets may cause adrenal insufficiency by decreasing the body's production of hormones called corticosteroids. Corticosteroids affect the body's balance of water and salts and minerals (electrolytes). Health care professionals should monitor adrenal function in patients taking Nizoral tablets who have existing adrenal problems or in patients who are under prolonged periods of stress such as those who have had a recent major surgery or who are under intensive care in the hospital.

Nizoral may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems. All medications that a patient is currently taking should be assessed for possible interactions with Nizoral tablets.

In summary, Nizoral's drug label now limits its usage by removing indications in which the risk outweighs the benefits. FDA has also approved a new patient Medication Guide informing about the potential risks associated with Nizoral tablets, which must be dispensed with every prescription for the drug.

News release, US FDA, 26 July 2013

METFORMIN AND PROSTATE CANCER

(Continued from page 1)

tively inexpensive. Previous research has focused on whether metformin might reduce the risk of getting prostate cancer, but most studies were negative. Some experts believe the drug instead works to improve survival once the cancer occurs.

In the new study, published online 5 August 2013 in the *Journal of Clinical Oncology*, Margel looked at more than 3,800 diabetic men aged 67 or older who lived in Ontario. About one-third were taking metformin at the study's start. Others were using different diabetes drugs. The men took metformin for a median of 19 months (half longer than that, half shorter) before the cancer was diagnosed and nearly nine months after.

During roughly four years of follow-up, Margel found those who took metformin had a 24 percent reduction in risk from prostate cancer death for every additional six months of use after their cancer diagnosis. The risk reduction of death from other causes was initially the same but declined over time. In both instances, although an association was found between metformin and survival, a direct cause-and-effect relationship was not established.

No reduction in death risk was seen for patients taking any other diabetes drug. Typical side effects of the drug are mild diarrhea and stomach problems, Margel said. "Usually they subside after one or two weeks," he said.

Although other diabetes drugs work by increasing the body's insulin production, metformin is an "insulin sensitizer" that works by making the body more sensitive to the insulin already produced. Insulin is needed to move glucose into cells for energy. Some research suggests that high insulin levels can influence cancer growth. Metformin, by not increasing the body's insulin production, may decrease cancer cells' growth, some experts say.

In their next study, the researchers plan to test metformin in patients with prostate cancer but not diabetes. "Metformin is very safe to use among nondiabetic patients," Margel said.

The findings point to a need for a large study in which men with early stage prostate cancer are assigned to a metformin group or placebo group, one expert said. Writing in an accompanying journal editorial, Kathryn Penney, an instructor in medicine at Brigham and Women's Hospital in Boston, said at least nine ongoing trials are looking at metformin in men with recurrent or advanced prostate cancer.

But these current trials might be starting too late, she said. Instead, a trial should look at metformin's effect at the time of diagnosis, when the disease is typically in early stages.

"If this trial showed a benefit, then yes, men without diabetes could be put on metformin at the time of prostate cancer diagnosis," she said.

HealthDay News, 5 August 2013

PROSTATE CANCER HORMONE TREATMENT: KIDNEY RISK?

Hormone therapy for prostate cancer may dramatically increase a man's risk of kidney failure, according to a new study. Canadian researchers found that the use of androgen deprivation therapy (ADT) was tied to a 250 percent increase in a man's chances of suffering acute kidney injury in a review of more than 10,000 men receiving treatment for early stage prostate cancer. The study appeared in the 17 July 2013 issue of the *Journal of the American Medical Association*.

ADT uses medication or surgery to reduce the amount of male hormones in a man's body, which can then cause prostate cancer cells to shrink or grow more slowly. It is a therapy usually reserved for advanced cases of prostate cancer, said study co-author Laurent Azoulay, a pharmacoepidemiologist at Jewish General Hospital's Lady Davis Institute, in Montreal. Previous research already has linked ADT to a possible increased risk of heart attack.

These new findings tying ADT to acute kidney injury – a rapid loss of kidney function with a 50 percent mortality rate – should prompt doctors to think twice before using ADT to treat prostate cancer patients at little risk of dying from the disease, said Azoulay, also an assistant professor in McGill University's department of oncology.

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KIDNEY INJURY WITH ADT

(Continued from page 5)

"There is a big debate over who should receive ADT, and the timing of use," he said. "In patients whose prostate cancer has spread, the benefits outweigh the risk, but now there's this jump to using [ADT] in patients who would not typically die from prostate cancer. In that subgroup of patients, the risks might outweigh the benefit."

Dr. Durado Brooks, director of prostate and colorectal cancers for the American Cancer Society, called the Canadian study "intriguing."

"They did find what would appear to be a fairly strong association between ADT and acute kidney injury," Brooks said. "This is something that men and their clinicians need to be aware of and watching out for if they choose to go with ADT as part of their treatment plan for prostate cancer."

However, Brooks also noted that the study relied on past medical data and did not involve current prostate cancer patients compared against a control group. "These results are suggestive that an association may exist, but they are not definitive," Brooks said. "There will need to be other research looking at this."

For the new study, the research team identified 10,250 men who had been diagnosed with nonmetastatic (not spreading) prostate cancer between 1997 and 2008, using patient data maintained by the UK. Researchers then tracked whether each patient had been hospitalized with acute kidney injury, and whether their kidney failure occurred during or after the hormone treatment.

Patients receiving ADT were 2.5 times more likely to suffer kidney failure, the study found. Risk particularly increased if combined androgen blockade was given, a therapy that uses different hormone-suppression methods to drastically decrease male and female hormone levels in the body.

"Testosterone and estrogen have been shown to play an important role in renal [kidney] function," Azoulay said. "It seems that testosterone has vessel-dilating effects, and estrogen has a protective effect against renal injury."

HealthDay News, 16 July 2013

SOY FAILS TO HALT PSA RISE IN PROSTATE CANCER

Soy supplementation had no effect on the risk of biochemical (PSA) recurrence (BCR) after radical prostatectomy (RP) in high-risk patients, investigators in a randomized trial reported online in the Journal of the American Medical Association (JAMA). The study ended early after an interim analysis showed a BCR rate of 27.2% in men who took the soy supplement versus 29.5% in men who received a calcium-derived control therapy. The results did not change in an analysis limited to adherent patients.

Several previous studies had examined the effect of soy protein on PSA levels in various populations of healthy men, men enrolled in surveillance for presumably indolent prostate cancer, men with high-grade prostatic intraepithelial neoplasia, and men with untreated prostate cancer. Collectively, the trials produced mixed and inconsistent results. No prior studies had evaluated soy's effect on BCR after RP.

In the study, Bosland and colleagues at 7 centers in the US enrolled men who had localized prostate cancer (T1c or T2) and a PSA value <0.07 ng/mL after RP. Eligible men had one or more high-risk features: PSA >20 ng/mL, final Gleason score ≥8, positive surgical margins, extracapsular extension, seminal vesicle invasion, or micrometastases in pelvic lymph nodes. Men were randomized to a soy protein isolate or a caseinate-based product, both incorporated into a beverage powder and consumed daily.

The primary endpoint was the 2-year rate of BCR and time to BCR. The investigators defined BCR as a serum PSA value ≥0.07 ng/mL, confirmed by 2 subsequent tests at least 1 month apart. Adherence was self-reported and monitored by serial measurement of serum genistein. The groups had similar rates of adverse events, and the principal reasons for discontinuation related to the taste and palatability of assigned treatment.

Investigators randomized 177 men from July 1997 to May 2010. The trial design called for an interim analysis after 45 BCR events. At the interim analysis, 22 of 81 (27.2%) evaluable men in the soy arm had BCR compared with 23 of 78 (29.5%) in the control group. The authors reported that 11 adherent participants discontinued treatment before the interim analysis but remained in follow-up. Exclusion of those patients in a per-protocol analysis did not change the results, nor did censoring of 13 participants considered possibly non-adherent because of serum genistein levels.

Despite the negative outcome, the investigators emphasized that the results apply only to a specific patient population. "The lack of protective activity of soy against prostate cancer recurrence observed in this study was limited to men at above-average risk of recurrence within the first 2 years after surgery and to the soy protein dose tested," Maarten C. Bosland, DVSc, PhD, of the University of Illinois at Chicago, and coauthors concluded in an article published online in JAMA. "The findings of this study may therefore not be generalizable to prostate cancer patients at average risk of recurrence."

The trial had limitations that go beyond generalizability, said Derek Raghavan, MD, PhD, of Carolinas HealthCare System in Charlotte, N.C., who was not involved in the trial. "This is a really disappointing study, because it was poorly designed and executed, and I don't think it tells us anything new," he added. The trial included men with various levels of risk, required 13 years to conduct, and enrolled relatively few men despite screening thousands of patients, he added.

"Half of the patients got what appears to be a poorly characterized soy product and the other half got a calcium caseinate product, which in other contexts is used as a source of energy in diet supplementation. It's really impossible to figure out whether those confounding factors would have made the study null and void," said Raghavan.

MedPage Today, 10 July 2013

DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD www.prostatevideos.com

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 A study by Margel and co-workers suggests that the diabetes drug, metformin might benefit men with prostate cancer (PCa). Their uncontrolled study found that diabetic men taking the drug survived longer than diabetics with PCa taking another available drug. The longer the drug was taken, the greater the benefit. This is an interesting observation, but as the article states, it does not prove direct cause and effect. That can only be determined by a prospective, randomized study. These preliminary findings appear to justify doing such a study. Deciding the optimal group of men to study is the challenge. The drug might be best if started at the time of diagnosis, but results could take 10 years and the study would be very costly. Testing men with more advanced disease would take less time but might be too late to provide a clinical benefit.

The Bottom Line: Metformin may be worth studying prospectively in men with PCa, although the challenge will be to select the best group of men to study.

a2p1c2 A working group organized by NCI recommends that pathologists stop calling high grade Prostatic Intraepithelial Neoplasia (HGPIN), a cancerous condition. By not calling it "cancer" NCI suggests that this may reduce interventions that do not offer men a real benefit. This certainly seems worthwhile, however, some doctors are also suggesting that we also stop using the "C" word for very low risk, Gleason 3+3 cancers that are now being diagnosed more frequently . The thinking is that not calling it cancer will encourage more men to accept active surveillance (AS) and avoid overtreatment. It is estimated that over 1 million men have been treated unnecessarily since PSA screening began. Faced with a diagnosis of even a very low risk cancer, most men and/or their 'significant other' will not accept AS and perhaps a change in wording would make that more acceptable. But, others argue that it would create potential liability for doctors if any of those men are misclassified, told they don't really have cancer, and then develop progressive disease.

The Bottom Line: Is it cancer or not? Men with a prostate biopsy showing HGPIN should avoid being alarmed.

a3p1c3 The FDA issued new warnings for the use of ketoconazole to treat fungal disease because of its potential to cause severe liver injury and adrenal insufficiency. This information is important for men with PCa because the drug is sometimes used to treat men with a rising PSA on androgen deprivation therapy (ADT). Fortunately, adrenal insufficiency rarely occurs because most doctors combine it with prednisone to prevent that problem. However, a potential for liver toxicity remains. Men should be aware that no study has shown this drug helps improve survival or delays metastatic disease, and the FDA has not approved its use for PCa. It does, however, lower PSA. Ketoconazole works in a similar way to abiraterone, but the latter is more effective and has been shown to improve survival. For men with a rising PSA after ADT who do not have metastases, they might consider participating in a Phase III clinical trial using a promising new drug called ARN-509 before trying ketoconazole, because they will be ineligible if they get ketoconazole first.

The Bottom Line: Ketoconazole has new warnings from the FDA and men should be aware it has not been approved for men with PCa nor has it been shown to offer a real clinical benefit.

a4p2c2 Is the glass half empty or half full? That is the question I think of when reading the report by Autio et al where they combined docetaxel and ^{153}samarium (^{153}Sm-EDTMP) in a small group of men with metastatic castration resistant PCa (mCRPC). They reported the results inappropriately based in part on a drop in the PSA. Unfortunately, a greatly reduced platelet count (thrombocytopenia) occurred in 30% of the men! This is likely to limit the ability to receive other chemotherapy such as cabazitaxel, which does improve survival. The authors concluded that ^{153}Sm-EDTMP "can be safely combined with docetaxel." My conclusion is that this is a very toxic therapy with no evidence of an impact on the disease. Time and time again, researchers use the PSA response to support their conclusion that a new therapy helps men with PCa even though the FDA does not accept it when evaluating any PCa therapy.

The Bottom Line: Men should be very cautious about receiving a combination of ^{153}Sm-EDTMP and docetaxel until much more evidence is provided to show it provides true clinical benefit.

a5p2c3 A small study by Dason, et al found that the onset of CRPC was delayed in men whose serum testosterone (T) declined and remained below 32 ng/dL with an LHRH agonist compared to men with T levels between 32 and 50 ng/dL. The FDA had defined a castrate T as ≤50 ng/dL because lower levels were not quantifiable. Since then, more sensitive T assays were developed and studies revealed that castrate levels ranged between 10-20 ng/dL. These results are consistent with another small, uncontrolled study reported years ago. Unfortunately, without a properly designed trial, the true importance of the T level cannot be determined. This finding does seem logical, however, because we now know that low T levels can stimulate some PCa cells. Until proper studies are done, men should consider asking their doctor to check the T level a few times a year to achieve maximum benefit from LHRH therapy regardless of the PSA. If T is above 32 ng/dL, consider changing to a different LHRH agonist, or to the antagonist, or be surgically castrated to further lower T levels.

The Bottom Line: The level of castrate T achieved with an LHRH agonist or antagonist might be more important than many doctors realize even when it is less than 50 ng/dL.

a10p6c2 The study by Bosland and co-workers also assessed outcome inappropriately using PSA. They conducted a randomized study comparing a soy supplement to a control in high-risk men

(Continued on page 8)

DOCTOR CHODAK'S BOTTOM LINE *(Continued from page 7)*

after radical prostatectomy (RP). The study was done because some uncontrolled studies have suggested that soy intake might benefit men with PCa. Although the design otherwise appeared appropriate, certain criticisms are raised by Dr. Raghavan. The fact that study accrual took a long time, however, is not by itself a reason to discount the results. A more appropriate criticism is their use of biochemical failure to assess soy's effectiveness. Without knowing the impact on survival or time to metastases, one cannot say if the treatment is helpful.

The Bottom Line: The usefulness of soy supplements in men with any stage of PCa remains unknown for now.

a8p4c1 In an article likely to upset many urology practices, the GAO has identified the potentially inappropriate self-referral of men with PCa to receive IMRT in facilities owned by urology group practices. Another study from Texas found that men were often having to travel an extra 30 miles per day (bypassing a center closer to their home) to receive RT from a center owned by the urologists. Men have every reason to be concerned about being advised to have IMRT, particularly since no study has shown any advantage of it compared to RP or brachytherapy (BT, seed implants). Also, many of the men getting IMRT would do just as well with AS. In fact, quality of life and patient convenience appears to favor BT over IMRT, and yet the use of this treatment has declined. One other fact; BT is far less profitable for urologists! One might justify IMRT machines owned by urologists if no RT center is located in the geographic area of men that need treatment. However, to date, that has not been the case. In the end, the bill being put through congress hopefully will get approved because it will be better for both patients and taxpayers.

The Bottom Line: Men advised to have IMRT should seek a second opinion if their urologist is part owner of a facility where this treatment will be administered.

a9p5c3 Another ADT study raising concerns was reported by Azoulay and associates. They conducted a large, retrospective analysis of men with PCa and found that those who were treated with ADT were 2.5 times more likely to suffer kidney failure than men not receiving ADT. Like other similarly designed studies, no valid conclusions can be made about cause and effect. Also, no randomized study comparing ADT to no ADT has ever identified this risk. Nevertheless, this new finding is worth further evaluation and all men on ADT should have their kidney function checked periodically. As the article points out, men should be more reluctant to go on ADT simply for a rising PSA because no study has ever shown a survival benefit unless metastatic disease is present. Also, doctors have become more aware of the many additional side effects from this therapy besides hot flashes and a decreased sex drive.

The Bottom Line: ADT is best used in men with evidence of metastatic disease where the benefits outweigh the risks. For those with a rising PSA and no metastases, the side effects may outweigh the benefits, especially because no study has shown that men live longer by starting it sooner.

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