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US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

OCTOBER 2012

US FDA APPROVES XTANDI® (ENZALUTAMIDE) AFTER PRIORITY REVIEW FOR PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PREVIOUSLY TREATED WITH DOCETAXEL

Medivation, Inc. and Astellas Pharma Inc. announced that the US Food and Drug Administration (FDA) has granted approval to Xtandi ® (enzalutamide) capsules for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. Xtandi is an oral, once -daily androgen receptor inhibitor.

The FDA accepted the Xtandi New Drug Application (NDA) on July 23, 2012, and granted the filing Priority Review Designation with a Prescription Drug User Fee Act (PDUFA) action date of November 22, 2012. Medivation and Astellas expect to make Xtandi available to patients in the United States in mid-September 2012, and the specific availability date will be announced on www.XtandiHCP.com as soon as it is known. Separately, a Marketing Authorization Application for Xtandi has been accepted for review by the European Medicines Agency (EMA).

"... Approval marks a significant accomplishment for Medivation. We are proud to be in a position to offer a new treatment, Xtandi , for this patient population for which there is a significant unmet medical need," said David Hung, MD, co-founder, president and CEO, Medivation, Inc. "I would like to extend my thanks to the patients, physicians, and their study teams who participated in the clinical trials, and to our employees, and those of our partner Astellas, who have been instrumental in helping us reach this important milestone."

"Enzalutamide provides an exciting new option for physicians that can prolong the lives of patients with metastatic prostate cancer who have received chemotherapy," said Howard I. Scher, MD, chief, Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, and the co-principal investigator of the AFFIRM pivotal study. "It is extremely gratifying to have led the clinical trial of enzalutamide, having followed the development of this drug from its early inception in the laboratory to the clinic."

"We believe Xtandi has the potential to play an important role in the treatment of advanced prostate cancer," said Stephen Eck, MD, PhD, Vice President of Medical Oncology, Astellas Pharma Global Development. "We're eager to work with Medivation to make this much-needed new treatment available to medical professionals and patients in September."

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ASPIRIN MAY PROLONG PROSTATE CANCER SURVIVAL

Taking a regular dose of aspirin (ASA) may help men treated for prostate cancer, either with radical prostatectomy (RP) or radiotherapy (RT), live longer, especially if they have the high risk form of the disease. This was the finding of a new study published online ahead of print in the *Journal of Clinical Oncology*.

There have been studies suggesting that regular ASA or other anticoagulants (ACs) can slow cancer growth and prevent it spreading. For instance, earlier this year, three studies in *The Lancet* added weight to the idea that for cancer, the benefits of daily ASA probably outweigh the risks. But clinical evidence has been limited, say Choe and colleagues.

The multicenter trial studied data on nearly 6,000 men who had prostate cancer treated with RP or RT and whose details were recorded in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database. Thirty-seven percent of the participants (about 2,200 men) were taking ACs (warfarin, clopidogrel, enoxaparin, and/or ASA). Researchers compared the risk of death from prostate cancer between the participants taking ACs and those who did not.

Results showed that the 10-year rate of prostate cancer-related death was significantly lower in the AC group than it was in the non-AC group (3% vs. 8%

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PROVENGE IMMUNE PARAMETERS CORRELATE WITH SURVIVAL: AN ANALYSIS OF THE RANDOMIZED PHASE 3 CLINICAL TRIALS IN MEN WITH CASTRATION-RESISTANT PROSTATE CANCER

Sheikh NA, Petrylak D, Kantoff PW, et al.

Cancer Immunol Immunother 3 August 2012; Epub

Purpose: Provenge (sipuleucel-T), the first FDA-approved autologous cellular immunotherapy for treatment of advanced prostate cancer, is manufactured by activating peripheral blood mononuclear cells, including antigen presenting cells (APCs), with a fusion protein containing prostatic acid phosphatase. Analysis of data from three phase 3 trials was performed to immunologically characterize this therapy during the course of the three doses, and to relate the immunological responses to overall survival (OS).

Methods: Sipuleucel-T product characteristics [APC numbers, APC activation (CD54 upregulation), and total nucleated cell (TNC) numbers] were assessed in three randomized, controlled phase 3 studies (N = 737). Antigen-specific cellular and humoral responses were assessed in a subset of subjects. Relationships between these parameters and OS were assessed.

Results: APC activation occurred in the first dose preparation [6.2-fold, (4.65, 7.70); median (25th, 75th percentile)] and increased in the second [10.6-fold (7.83, 13.65)] and third [10.5-fold (7.89, 13.65)] dose preparations. Cytokines and chemokines associated with activated APCs were produced during the manufacture of each dose; T-cell activation-associated cytokines were detected in the second and third dose preparations. Antigen-specific T cells were detectable after administration of the first sipuleucel-T dose. Cumulative APC activation, APC number, and TNC number correlated with OS ($P < 0.05$). Antigen-specific immune responses were observed in 78.8 % of monitored subjects and their presence correlated with OS ($P = 0.003$).

Conclusion: Sipuleucel-T broadly engages the immune system by activating APCs ex vivo and inducing long-lived immune responses in vivo. These data indicate antigen-specific immune activation as a mechanism by which sipuleucel-T prolongs OS.

AN UPDATED PROSTATE CANCER STAGING NOMOGRAM (PARTIN TABLES) BASED ON CASES FROM 2006 TO 2011

Eifler JB, Feng Z, Lin BM, et al

BJU Int 26 July 2012; Epub

Pathological stage after radical prostatectomy (RP) can be accurately predicted by serum PSA, clinical stage and biopsy Gleason sum, the 'Partin tables.' Since the previous publication of the Partin tables, an updated Gleason scoring system has been established and incremental changes have occurred in the clinical characteristics of patients diagnosed with prostate cancer. The current analysis updates the Partin nomogram in a contemporary cohort of patients.

Objective: To update the 2007 Partin tables in a contemporary patient population.

Patients and methods: The study population consisted of 5,629 consecutive men who underwent RP and staging lymphadenectomy at the Johns Hopkins Hospital between January 1, 2006 and July 30, 2011 and met inclusion criteria. Polychotomous logistic regression analysis was used to predict the probability of each pathologic stage category: organ-confined disease (OC), extraprostatic extension (EPE), seminal vesicle involvement (SV+), or lymph node involvement (LN+) based on preoperative criteria. Preoperative variables included biopsy Gleason score (6, 3+4, 4+3, 8, and 9-10), serum PSA (0-2.5, 2.6-4.0, 4.1-6.0, 6.1-10.0, >10.0 ng/mL), and clinical stage (T1c, T2c, and T2b/T2c). Bootstrap re-sampling with 1,000 replications was performed to estimate 95% confidence intervals for predicted probabilities of each pathologic state.

Results: The median PSA was 4.9 ng/mL; 63% had Gleason 6 disease, and 78% of men had T1c disease. Seventy-three percent of patients had OC disease; 23% had EPE; 3% had SV+ but not LN+, and 1% had LN+ disease. Compared to the previous Partin nomogram, there was no change in the distribution of pathologic state. The risk of LN+ disease was significantly higher for tumors with biopsy Gleason 9-10 than Gleason 8 (OR 3.2, 95% CI 1.3-7.6).

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INTERMITTENT ANDROGEN SUPPRESSION FOR RISING PSA LEVEL AFTER RADIOTHERAPY

Crook J, O'Callaghan C, Duncan G, et al

N Engl J Med 2012; 367: 895-903

Background: Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial.

Methods: We enrolled patients with a PSA level greater than 3 ng per milliliter more than 1 year after primary or salvage radiotherapy for localized prostate cancer. Intermittent treatment was provided in 8-month cycles, with nontreatment periods determined according to the PSA level. The primary end point was overall survival. Secondary end points included quality of life, time to castration-resistant disease, and duration of nontreatment intervals.

Results: Of 1386 enrolled patients, 690 were randomly assigned to intermittent therapy and 696 to continuous therapy. Median follow-up was 6.9 years. There were no significant between-group differences in adverse events. In the intermittent-therapy group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent therapy provided potential benefits with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function. There were 268 deaths in the intermittent-therapy group and 256 in the continuous-therapy group. Median overall survival was 8.8 years in the intermittent-therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86 to 1.21). The estimated 7-year cumulative rates of disease-related death were 18% and 15% in the two groups, respectively (P=0.24).

Conclusions: Intermittent androgen deprivation was noninferior to continuous therapy with respect to overall survival. Some quality-of-life factors improved with intermittent therapy.

OUTCOMES OF INITIALLY EXPECTANTLY MANAGED PATIENTS WITH LOW OR INTERMEDIATE RISK SCREEN-DETECTED LOCALIZED PROSTATE CANCER

Bul M, van den Bergh RCN, Zhu X, et al

BJU Int, 29 August 2012; Epub

What's known on the subject and what does the study add?

Active surveillance (AS) aims to reduce overtreatment by selecting patients with low risk prostate cancer (PCa) based on favourable disease characteristics. However, most studies on AS do not have long-term results available; in particular, data on patients with intermediate risk disease are lacking.

Our findings demonstrate that withholding radical treatment in men with low or intermediate risk screen-detected localized PCa leads to a substantial delay or even avoidance of radical treatment in a majority of men. Favourable disease-specific outcomes confirm the feasibility of AS for low risk PCa and also support a role for AS in selected patients with intermediate risk PCa.

Objective: To assess the longer-term feasibility of AS, we aimed to evaluate outcomes of patients with screen-detected localized prostate cancer (PCa) who initially elected to withhold radical treatment for either low or intermediate risk disease.

Patients and Methods: All men underwent screening for PCa in the Rotterdam and Helsinki arms of the European Randomized Study of Screening for Prostate Cancer (ERSPC); eligible men were diagnosed with PCa prior to the establishment of the ERSPC-affiliated Prostate Cancer Research International: Active Surveillance (PRIAS) study (1994–2007) and were initially expectantly managed in the absence of a fixed follow-up protocol. Low risk PCa was defined as clinical stage T1/T2, PSA ≤10 ng/mL, PSA density <0.2 ng/mL/mL, Gleason ≤6 and maximum two positive biopsy cores, whereas PSA 10–20 ng/mL, Gleason score 7 and three positive biopsy cores were considered intermediate risk features. Disease-specific, overall and treatment-free survival were analysed using the Kaplan–Meier and competing risks methods.

Results: In all, 509 patients with PCa were eligible, of whom 381 were considered low risk and 128 intermediate risk. During a median follow-up of 7.4 years, a total of 221 patients (43.4%) switched to deferred treatment after a median of 2.6 years. The calculated 10-year disease-specific survival rates were 99.1% and 96.1% for low and intermediate risk patients, respectively (P= 0.44), and for overall survival 79.0% and 64.5%, respectively (P= 0.003). Competing risks analysis showed similar results.

Conclusions: Withholding radical treatment in men with low to intermediate risk screen-detected PCa leads to a substantial delay or even avoidance of radical treatment and its potential side-effects in a majority of patients. Disease-specific outcomes at 7.4 years of follow-up are favourable in low as well as intermediate risk patients. This confirms the feasibility of AS according to contemporary criteria, and also suggests a potential role for AS in selected men with intermediate risk features.

US TOO SEEKS BOARD MEMBER APPLICATIONS

Us TOO International, is seeking qualified individuals to serve on its Board of Directors. Members have been diagnosed with prostate cancer, are a member of such a man's family or significant other, or any person involved in or interested in support or treatment of such patients. Other qualifications include familiarity with an Us TOO chapter, ability to think globally, skills or experience deemed beneficial to the work of Us TOO and commitment to Us TOO's purpose and mission.

See details at www.ustoo.org/SeekBoardMembers.asp. Send letters of nomination with a vita or resume to Thomas Kirk, President and CEO, Us TOO International, 5003 Fairview Avenue, Downers Grove, IL 60515 or e-mail tom@ustoo.org.

STUDY 'SHOWS THE WAY' TO RESOLVING PSA CONTROVERSY

Quality-Adjusted Life-Years Are Key

A new approach to evaluating the benefits and harms of PSA testing "shows the way to a resolution of the long-standing problem about screening for prostate cancer," according to an editorial in the August 16th edition of *The New England Journal of Medicine* (Vol. 367, pp. 595-605, 2012). "This is welcome news," says editorialist Harold Sox, MD, because the conflicting results from major American and European randomized trials of the screening "did not settle the matter."

A big part of the problem has been that any recommendation about testing, like that recently from the US Preventive Services Task Force, is based on an "apples-and-oranges" comparison, says Dr. Sox, who is from the Dartmouth Institute for Health Policy & Clinical Practice, in Hanover, NH. The units of measure are different for benefits (cancer deaths averted) compared with those for harms (overtreatment, erectile dysfunction, urinary problems), he points out.

A new study, published in tandem with the editorial, now addresses the "apples-and-oranges problem" by using the same measure – quality-adjusted life-years (QALYs) – to quantify the harms and benefits of screening, Dr. Sox explains. "Because the authors express harms and benefits in the same units, they could calculate net benefit, an objective measure of the balance of harms and benefits," he writes.

To determine quality of life, the authors used "utility estimates" for various health states, such as undergoing a screening test or being treated with radical prostatectomy (RP) or terminal illness. They predicted the number of QALYs associated with screening by using these utility estimates, which were obtained from other studies.

The new study, which is derived from statistical modeling, found that the benefit of prostate cancer screening is "diminished" by the loss of quality-adjusted life-years caused by overdiagnosis and overtreatment. Nevertheless, there is an average net benefit from

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US FDA APPROVES XTANDI® *(Continued from page 1)*

The recommended dose of Xtandi is 160 mg (four 40 mg capsules) administered orally once daily. Xtandi can be taken with or without food and does not require concomitant steroid (e.g., prednisone) use. In the phase 3 clinical trial, 48% of Xtandi patients and 46% of patients in the placebo arm were treated with glucocorticoids.

As a post-marketing requirement, Medivation and Astellas have agreed with the FDA to conduct an open-label safety study of Xtandi (160 mg/day) in patients who are at high risk for seizure.

The efficacy and safety of Xtandi were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. A total of 1,199 patients with mCRPC who had previously received docetaxel were randomized 2:1 to receive either Xtandi orally at a dose of 160 mg once daily (N = 800) or placebo (N = 399). Patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizure were excluded from the clinical trial. The primary endpoint of the trial was overall survival.

Xtandi-treated patients had a statistically significant improvement in median overall survival compared to the placebo group: 18.4 months in the Xtandi group versus 13.6 months in the placebo group ($P<0.0001$). Xtandi provided a 37% reduction in risk of death compared to placebo (hazard ratio = 0.631). Seizure occurred in 0.9% of patients on Xtandi and 0% of the placebo-treated patients. Grade 3 and higher adverse reactions were reported among 47% of Xtandi - treated patients and 53% of placebo-treated patients.

Xtandi is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Xtandi has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. Xtandi decreased proliferation and induced cell death of prostate cancer cells in vitro and decreased tumor volume in a mouse prostate cancer xenograft model.

Important Safety Information

Contraindications: Xtandi can cause fetal harm when given to pregnant women based on its mechanism of action. It is not indicated for use in women and is contraindicated in women who are or may become pregnant.

Warning and Precautions: In the randomized clinical trial, seizure occurred in 0.9% of patients on Xtandi. No patients on the placebo arm experienced seizure. Because of the risk of seizure associated with Xtandi use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Adverse Reactions: The most common adverse drug reactions (≥ 5%) reported in patients receiving Xtandi in the randomized clinical trial were asthenia/ fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension.

Drug Interactions: Enzalutamide is an inducer of livers enzyme that are important for the breakdown and elimination of drugs in humans. As such, several important interactions can occur with co -administration of certain drugs that can increase or decrease Xtandi blood levels. Please be sure to tell your doctor the names of all of the medications you are currently taking before starting Xtandi treatment.

For Full Prescribing Information, please visit www.XtandiHCP.com.

Medivation/Astellas Pharma News Release, 31 August 2012

Want to learn more about local prostate cancer support group activities? Read the

CHAPTER NEWS!

at www.ustoo.org!

QUALITY-ADJUSTED LIFE-YEARS

(Continued from page 4)

screening in terms of QALYs, according to the study authors, who are led by Eveline Heijnsdijk, PhD, of the Erasmus Medical Center in the Netherlands.

Inputting data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and other sources into their model, Dr. Heijnsdijk and colleagues found that, for 1000 men of all ages who were followed-up for their entire life span, annual screening of those between the ages of 55 and 69 years would result in:

- 9 fewer deaths from prostate cancer (28% mortality reduction);
- 14 fewer men receiving palliative therapy (35% reduction); and
- 73 total life-years gained (average 8.4 per prostate cancer death avoided).

However, the total number of (QALYs) gained from screening that group was lower (56 years) than the unadjusted (73 years) because of harms due to screening, they report. Screening would also result in 45 men being overdiagnosed and overtreated. The authors calculated that to prevent 1 prostate cancer death, 98 men would have to be screened and 5 cancers would have to be detected.

These numbers are "more favorable" than the 1,068 and 48 reported in earlier ERSPC results, say the authors. But their model "predicts long-term effects after a much longer period," they claim, which would allow the control group to have more cancers detected and disease-specific deaths to occur.

These results from the new study are not the final word on evaluating prostate cancer screening because even longer follow-up data are needed from the ERSPC and from quality-of-life analyses. Until longer-term data are available, "universal recommendations regarding screening" should not be made, they conclude.

Dr. Sox agrees, but for different reasons. He finds fault in technical details of the modeling and states that, until more work is done to refine this kind of modeling, "guidelines should avoid recommending for or against PSA screening."

Medscape Medical News, 15 August 2012

RANDOMISED CONTROLLED TRIAL COMPARING LAPAROSCOPIC AND ROBOT-ASSISTED RADICAL PROSTATECTOMY

Porpiglia F, Morra I, Lucci Chiarissi M, et al

Eur Urol 20 July 2012; Epub

Objective: To compare RARP and LRP in terms of the functional, perioperative, and oncologic outcomes. The main end point of the study was changes in continence 3 months after surgery.

Design, Setting, and Participants: From January 2010 to January 2011, 120 patients with organ-confined prostate cancer were enrolled and randomly assigned (using a randomisation plan) to one of two groups based on surgical approach: the RARP group and the LRP group.

Intervention: All RARP and LRP interventions were performed with the same technique by the same single surgeon.

Outcome Measurements and Statistical Analysis: The demographic, perioperative, and pathologic results, such as the complications and PSA measurements, were recorded and compared. Continence was evaluated at the time of catheter removal and 48 hours later, and continence and potency were evaluated after 1, 3, 6, and 12 months The student t test, Mann-Whitney test, χ^2 test, Pearson χ^2test, and multiple regression analysis were used for statistics.

Results and Limitations: The two groups (RARP: n=60; LRP: n=60) were comparable in terms of demographic data. No differences were recorded in terms of perioperative and pathologic results, complication rate, or PSA measurements. The continence rate was higher in the RARP group at every time point: Continence after 3 mo was 80% in the RARP group and 61.6% in the LRP group (p=0.044), and after 1 yr, the continence rate was 95.0% and 83.3%, respectively (p=0.042). Among preoperative potent patients treated with nerve-sparing techniques, the rate of erection recovery was 80.0% and 54.2%, respectively (p=0.020). The limitations included the small number of patients.

Conclusions: RARP provided better functional results in terms of the recovery of continence and potency. Further studies are needed to confirm our results.

LOW ACCURACY OF ROUTINE ULTRASOUND-GUIDED SYSTEMATIC 12-CORE BIOPSIES IN PROSTATE TUMOR MAPPING

Belas O, Hupertan V, Comperat E, et al

Can J Urol 2012; 19: 6366-72

Introduction: To determine the accuracy of a 12-core biopsy protocol in assessing the location of prostate tumors within radical prostatectomy (RP) specimens.

Materials and Methods: A consecutive series of patients with T1c stage prostate cancer who had undergone 12 ultrasound-guided prostate biopsies prior to RP was considered. The locations of the biopsies from prostate gland mapping were compared with the locations of tumor tissues obtained after analysis of the prostate specimens.

Results: Overall, 78 patients (27.4%) were included. The median PSA level was 6 ng/mL. The median prostate weight was 45 g (range 22 to 102). Overall, 936 biopsies were performed in the 78 men, of which 254 biopsies were positive. The mean number of positive biopsies per patient was 3.7 (range 1 to 12). Pathologic examination of the surgical specimens revealed that 58 (74.4%) patients had pT2 disease and 20 patients (25.6%) had locally advanced disease (pT3). The biopsy protocol's sensitivity, specificity and positive predictive value for tumor location were 0.34, 0.83 and 0.84. The performance of the protocol was modest in assessing the exact tumor location (area under curve (AUC) 0.581, 95% confidence interval (CI) 0.489-0.719).

Conclusions: Routine, ultrasound-guided, systematic 12-core biopsies lack precision in prostate tumor mapping.

GENETIC LINK TO PROSTATE CANCER RISK IN AFRICAN AMERICANS FOUND

Prostate cancer in African-American men is associated with specific changes in the IL-16 gene, according to researchers at the University of Illinois at Chicago College of Medicine. The study, published online in the journal *Cancer Epidemiology, Biomarkers & Prevention*, establishes the association of IL-16 with prostate cancer in men of both African and European descent.

Previously identified changes in the gene for IL-16, an immune system protein, were associated with prostate cancer in men of European descent. But the same changes in the gene's coded sequence – called "polymorphisms" – did not confer the same risk in African Americans. Doubt was cast on IL-16's role in prostate cancer when researchers were unable to confirm that the IL-16 polymorphisms identified in whites were also important risk factors in African Americans, Kittles said.

Kittles and colleagues used a technique called imputation – a type of statistical extrapolation – that allowed them to see new patterns of association and identify new places in the gene to look for polymorphisms. They found changes elsewhere in the IL-16 gene that were associated with prostate cancer and that were unique to African Americans.

Polymorphisms result from DNA mutations emerging in the ancestral history of different populations. People of African descent are much more genetically diverse than whites, Kittles said, making the search for polymorphisms associated with disease more difficult. Although the effect of the particular changes to the gene appear to be different in men of African versus European descent, it is likely that several of the polymorphisms in the gene alter the function of the IL-16 protein.

"This confirms the importance of IL-16 in prostate cancer and leads us in a new direction," Kittles said. "Very little research has been done on IL-16, so not much is known about it. We now need to explore the functional role of IL-16 to understand the role it is playing in prostate cancer," he said.

Science Daily, 31 August 2012

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

"The testosterone blood test should probably be a fasting blood test just like the cholesterol blood test."

Mark A. Moyad, MD, MPH
University of Michigan Medical Center, Department 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: Several new studies are suggesting that the accuracy of the testosterone blood test can be impacted by what you eat and other factors, which means it is probably time to fast (no food or beverages other than water for 9 -12 hours) the next time you get this blood test (yet this may not apply to men on testosterone suppression treatment for prostate cancer).

The Michigan versus Alabama football game last month was more painful than 1000 acupuncture needles placed in my testicular region (aka groin area)! Anyway, speaking of the testicles, which produce most of the testosterone that circulates in a man's body (wow-another great and realistic segue by Moyad), there are some new studies to suggest men need to fast before they get an early morning testosterone blood test!

Researchers studied 74 men with an average age of 51 years and they were given a standard dose of sugar from food and beverages and their blood was drawn at 0, 30, 60, 90, and 120 minutes.[1] Ingestion of sugar was associated with a significant (P <0.0001) 25% reduction in mean testosterone levels, which remained suppressed 120 minutes later. These results did not differ based on the body mass index or health of the men. A total of 15% of the men with normal testosterone levels experienced reductions in the hypogonadal (abnormally low) range at one or more time points. Thus, because of this and other studies, testosterone blood levels not only should be drawn in the early morning but probably should be drawn under fasting conditions now!

I have told men getting their PSA for years that they should get their cholesterol blood test and testosterone test the same morning to reduce the hassle of another blood draw. However, I had no idea that something as simple as "sugar" or in reality glucose or another aspect of dietary intake could influence this test so dramatically (otherwise I would have taken credit for it like the ego maniac that I am)! Still, think about this for a second….aging, sleep deprivation, extreme cholesterol reduction, excessive exercise, insulin resistance, and weight gain all can reduce testosterone levels!

Look, I just spent 20 minutes before typing this review searching the internet about the question of fasting and testosterone (yes, I know my life is pathetic and the Internet is about as accurate as a politician hooked up to a polygraph test) and virtually every site says the exact same thing, that you do not need to fast for the testosterone test. Another study from Australia just released showed that men ages 40-97 years had higher testosterone levels in the fasting state, and there is enough research to suggest that any large meal in the morning may reduce testosterone. The exception to this may be men on testosterone suppression treatment for prostate cancer because the drug is so powerful that it may be difficult to change your level of testosterone while on these medications.

Yet, who knows for sure, but the bottom line is that you should ask your doctor about this latest and craziest new information on the testosterone blood test. The old adage "you are what you eat" may now be taking on a whole new meaning in medicine my friends! Man, I love this stuff!

Reference

1. Caronia LM, Dwyer AA, Hayden D, et al: Clin Endocrinol (Oxf) 2012;

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

Editor: 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 There is now more good news for patients with metastatic disease. Enzalutamide (Xtandi ®) was FDA approved for men who progressed after docetaxel chemotherapy. Now the real challenge is determining the optimal way to use the available options that include Xtandi, abiraterone (Zytiga®), and very soon, ^{223}Radium (Alpharadin®). Definitive studies testing combinations of these drugs probably are unlikely to be conducted, at least in the near future. That will mean there will be considerable variability in which treatment doctors recommend first, second, third, etc. Both the side effect profile and ease of administration are likely to result in Xtandi and Zytiga being used first and or second or vice-versa. But many questions will remain such as whether men will respond as well to the second drug after the first one fails. Another very important question is whether using the two drugs at the same time could deliver even better results than giving one of them followed by the other at the time of progression.

The Bottom Line: Although curing metastatic prostate cancer is still a rare event, the availability of the various new options has increased the survival time for men not cured by local therapy.

a2p1c3 The latest study assessing the impact of anticoagulants, and in particular, aspirin on prostate cancer survival, is quite interesting but unfortunately not definitive. The CaPSURE database is not a controlled study and for that reason there are many reasons why the findings may not be correct. Certainly, on the basis of this report, it would be incorrect to recommend that men with prostate cancer, particularly high-grade disease, start taking aspirin to improve their outcome. For those who need it for their heart health, they may derive some additional benefit if they also have prostate cancer. What we hope, however, is that either the National Cancer Institute or any of the various research groups use these results to initiate a well-controlled trial that attempts to prove if anticoagulants and aspirin indeed benefit men with prostate cancer.

The Bottom Line: Here we have another uncontrolled study suggesting a benefit from anticoagulants but only a properly done prospective, randomized trial will be able to determine if this is truly a treatment that should be recommended to patients.

a3p2c2 The study involving Provenge® provides additional information in support of this therapy. Many doctors have been reluctant to recommend Provenge because the PSA does not decline and objective responses are rarely seen. For that reason, doctors seem to question if the treatment really works despite the randomized studies showing an improved survival. The study by Sheikh and co-workers provides support for this novel therapy by demonstrating that survival was significantly better in those men who developed an immune response such as T-cell activation, APC activation and the number of APC cells. Other recent data supporting the value of Provenge that has been presented at several meetings is the demonstration that the improvement in overall survival was much higher in men with a low vs. high PSA at the time of treatment.

The Bottom Line: Provenge is the first immunotherapy available for treating progressive metastatic prostate cancer and it appears that the patients most likely to respond are those who develop an immune response and also those who have the least amount of disease. Men with minimally symptomatic or asymptomatic progressive disease should discuss this option with their doctor in cases where it has not been offered.

a4p2c3 The report by Eifler et al. provides another update to the very valuable information provided by the Partin tables. Since the first time this information was published, it has been a useful tool for making treatment decisions in men with localized disease. One of the more valuable tools has been to decide whether or not to remove pelvic lymph nodes during radical prostatectomy (RP). Doing so does lengthen the operation and increase the risk of complications slightly yet many doctors continue to do it despite a VERY small chance of helping patients. This updated report further shows that the vast majority of men with newly diagnosed disease rarely have positive nodes, making a lymph node dissection a waste of time and money.

The Bottom Line: Any man diagnosed with a Gleason 3+3 or 3+4 cancer and a PSA under 10 ng/mL who decides to undergo RP should ask if a lymph node dissection will be performed. He should then actively discourage their surgeon from doing so because the odds of benefitting him are near zero.

a5p3c1 Another very important study just published deals with intermittent ADT (IADT) in men with a rising PSA after radiotherapy (RT). As discussed in a previous issue of the *HotSheet*, men with metastatic disease who receive IADT have a higher chance of dying from prostate cancer compared to men on continuous ADT (CADT) but there is no difference in overall survival. The well done randomized study by Crook et al found IADT for a rising PSA does not appear to result in a greater chance of dying from prostate cancer but it does offer some quality of life advantages.

The Bottom Line: Men who develop a rising PSA after RT and have no evidence of metastases should discuss the possibility of receiving IADT rather than CADT.

a6p3c2 Although the idea of active surveillance (AS) after a diagnosis of prostate cancer is very hard for most men to accept, the fact is that it may be the best course of action for many of them. The uncontrolled study by Bul and co-workers provides additional evidence that the risk associated with AS appears to be low, at least at ten years. This was true for men with low risk and also intermediate risk disease. This report is important because many physicians who are against AS argue that nearly 30% of men thought to have low risk prostate cancer actually have intermediate risk disease. This report shows that the projected risk of dying from intermediate-risk prostate cancer in 10 years is only ~4% when treated with AS. Clearly, longer follow-

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UPDATED PARTIN TABLES

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The c-indexes for EPE vs. OC, SV+ vs. OC, and LN+ vs. OC were 0.702, 0.853, and 0.917, respectively. Men with biopsy Gleason 4+3 and Gleason 8 had similar predicted probabilities for all pathologic stages. Most men presenting with Gleason 6 disease or Gleason 3+4 disease have < 2% risk of harboring LN+ disease and may have lymphadenectomy omitted at RP.

Conclusions: The distribution of pathologic stages did not change at our institution between 2000-2005 and 2006-2011. The updated Partin nomogram takes into account the updated Gleason scoring system and may be more accurate for contemporary patients diagnosed with prostate cancer.

THE BOTTOM LINE *(Continued from page 7)*

up in a larger number of patients will be necessary to better define the risk, but this is a step in the right direction.

The Bottom Line: This study provides some additional evidence in support of AS low and intermediate risk disease.

a7p4c1 To screen or not to screen, that is the question. Another study attempts to shed light on this controversy by determining the quality adjusted life years (QALY) that might result from either approach. The authors of this study argue that the benefits of screening are more favorable than suggested by the US task force report. Readers should beware of the problems of QALY analysis mainly because researchers try to put a number to various outcomes that is highly subjective. For example, if a healthy, sexually active man becomes impotent and has to live the rest of his life that way, how much does it subtract from his overall well-being? Is it 10%, 20% or 50%? The problem with mathematical models is that they don't reflect that each person is likely to assign a different value to the various outcomes that can occur. Perhaps the only thing to do to help a man decide if he wants to be screened is to complete a questionnaire asking about his own values for each health state and then calculate whether screening would be right for him. Generalizations like this are flawed.

THE BOTTOM LINE: Screening is likely to remain controversial for many years and these hypothetical analyses are interesting but ultimately not very help-

ASPIRIN

(Continued from page 1)

respectively). The risk of the cancer returning, and of it spreading to the bone was also significantly lower in the AC group.

Subgroup analysis of participants according to clinical risk showed the reduction in prostate cancer death was most pronounced in men with high-risk disease (4% v 19%, respectively). On further analysis, the reduction in prostate cancer death was mostly due to ASA.

They conclude that AC therapy, and ASA in particular, is linked with a reduced risk of death from prostate cancer in men treated either with RP or RT.

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