DNA Test Identifies Men with Six-Fold Increased Risk of Prostate Cancer

A major new study of more than 140,000 men has identified 63 new genetic variations in the DNA code that increase the risk of prostate cancer. These findings were published in the New England Journal of Medicine.

Researchers devised a new test combining these single-letter genetic variants with more than 100 others previously linked to prostate cancer to predict which men were most at risk of developing the disease during their lifetime. The test identifies 1% of men who are at highest risk because they have inherited many of these risky variants - and they are nearly six times more likely to develop prostate cancer than the population average.

Researchers identified new variants in DNA which, when inherited, increased a man's risk of prostate cancer. Each variant individually had only a small effect on risk, but the combined effect of inheriting multiple variants could be dramatic.

(Continued on page 3)

Prostate Cancer Vaccine, Prostvac-V/F, Found Not to Improve Survival

Prostvac-V/F, an investigational prostate cancer (PCa) vaccine regimen, does not improve overall survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), according to the findings of the phase 3 PROSPECT trial presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

The latest findings failed to confirm an overall survival (OS) benefit found in a previous randomized phase 2 trial (RandPh2). In that earlier trial, Prostvac-treated patients had a median OS that was significant greater than OS in placebo recipients (25.1 vs. 16.6 months). Prostvac-V/F consists of a recombinant vaccinia vector as a primary vaccination, followed by six booster doses with a recombinant fowlpox vector.

In the PROSPECT trial, James L. Gulley, MD, of the National Cancer Institute in Bethesda, MD, and colleagues, randomly assigned 1,297 men from 15 countries to receive either Prostvac-V/F plus placebo, Prostvac-V/F plus GM-CSF (granulocyte-macrophage colony-stimulating factor), or placebo plus placebo. Median OS for the groups was 34.8, 33.9, and 34.7 months, respectively. The differences between the Prostvac-V/F-placebo and placebo-placebo groups and Prostvac-V/F-GM-CSF and placebo-placebo groups did not differ significantly (Hazard Ratio [HR] 1.02; P=0.40 and HR 1.03; P=0.66, respectively).

Dr. Gulley's group noted in their study abstract that the OS compare more than half a million single-letter changes in the DNA code of nearly 80,000 men with prostate cancer and more than 61,000 men without the disease.

The researchers identified 63 new variants in DNA which, when inherited, increased a man's risk of prostate cancer. Each variant individually had only a small effect on risk, but the combined effect of inheriting multiple variants could be dramatic.

(Continued on page 8)

Enzalutamide Postpones Metastasis for a Subset of High-Risk Patients with Prostate Cancer

The median metastasis-free survival time for men with non-metastatic castration-resistant prostate cancer and rising PSA levels treated with enzalutamide was nearly double that of the median metastasis-free survival time for men in the same group treated with placebo (36.6 months vs. 14.7 months, respectively, P=0.001, a statistically significant difference), according to research published in the New England Journal of Medicine (Vol. 378, pp. 2465-2474, 2018).

Though researchers determined treatment with enzalutamide cut the risk of metastasis or death by 71%, median overall survival was not reached in either the enzalutamide or placebo group. While risk of death was 20% lower in the enzalutamide group vs. the placebo group, the result was not statistically significant.

Subjects were randomly assigned in a 2:1 ratio to receive either a 160 mg dose of enzalutamide or placebo once daily. Of the 1,401 men in the trial, 219 of 933 participants (23%) in the enzalutamide arm experienced metastasis or died, compared with 228 of 468 men (49%) in the placebo group. The study completion date was June 28, 2017, approximately four years after the study was initiated.

Men in the enzalutamide group demonstrated a longer time until the first use of a follow-up treatment with anticancer medications, and
A Randomized Phase III Trial Between Adjuvant Docetaxel and Surveillance After Radical Radiotherapy for Intermediate and High-Risk Prostate Cancer: Results of SPCG-13 Trial Clinical Trial NTC006653848

J Clin Oncol 36, 2018 (suppl; abstract 5000)

Background: Docetaxel combined with androgen deprivation therapy (ADT) has improved survival in advanced prostate cancer (APCa). This randomized trial evaluates if six courses of docetaxel improves biochemical disease-free survival (BDFS) after radical radiotherapy (RT) for intermediate- or high-risk PCa.

Methods: A total of 376 men were randomised in this multinational phase III study, to receive either six cycles of adjuvant docetaxel 75mg/m² every three weeks without continuous prednisone (Arm A, N=188) or surveillance (Arm B, N=188) after RT. Neoadjuvant/adjuvant ADT was mandatory for all patients. Primary end-point was a rising PSA ≥2ng/mL above the nadir PSA value. Intermediate- or high-risk prostate cancer was defined as T2 with Gleason score (GS) 4+3, PSA > 10; T2, GS 8-10 any PSA; or any T3. Men were followed for five years with PSA every three months for two years and thereafter every six months. Study power was 89% to detect a difference between groups and the sample size calculation accounted for T2/T3 distribution (12%/15% difference in BDFS was assumed for T2/T3 patients).

Results: All six cycles were completed in 147 (78.2%) of men in Arm A. Mean age in Arm A and Arm B was 66.2 and 66.4 years, respectively; 75.0% had T3 disease, 46.3% had GS 8-10. Median follow up was 59.4 months (range 1 to 111 months). The primary endpoint was reached in 30.7% of men; 31.0% in Arm A and 30.3% in Arm B. In a Kaplan-Meier analysis there showed no difference between the BDFS curves (p=0.631) between treatment groups. Febrile neutropenia occurred in 16.1% of docetaxel patients. No deaths were related to docetaxel treatment. There were 43 deaths during the trial (20 in Arm A and 23 in Arm B) of which nine and seven were due to PCa. In a Cox multivariate analysis, GS (p=0.001) was a significant predictor of PSA progression. Hazard Ratio for Arm A (docetaxel) vs. Arm B (surveillance) was 1.14 (95% CI 0.79 to 1.64, p = 0.495 not a statistically significant difference).

Conclusions: Adjuvant docetaxel without prednisone did not improve BDFS after radical radiotherapy with ADT for intermediate- or high-risk prostate cancer.
Clinical trial information: NTC006653848.

Statin Use and Time to Progression in Men on Active Surveillance for PCa

Prostate Cancer Prostatic Dis, 6 June 2018; Epub

Purpose: Recent evidence suggests that statins may improve prostate cancer outcomes; however, their role in active surveillance (AS) is poorly characterized. We aimed to evaluate the association between statin use at diagnosis and time to progression on AS.

Materials and Methods: Data were obtained from a prospectively maintained cohort of men undergoing AS between 1995 and 2016 at our institution. All men satisfied the low-risk criteria: Gleason score ≤7, ≤4 positive cores, <50% involvement of any core, and PSA level <10.0 ng/dL. Kaplan-Meier curves and multivariable Cox proportional hazards were used to assess statin exposure at diagnosis and at time to pathological progression (failing to meet the low-risk criteria at biopsy) and therapeutic progression (first of pathological progression or initiation of definitive therapy). Reclassification at confirmatory biopsy (first post-diagnostic biopsy) and progression beyond confirmatory biopsy were evaluated independently.

Results: Low-risk criteria were met by 797 men. Reclassification at the confirmatory biopsy occurred in 194 (24%) men, 51 (26%) of whom were statin users. Statin use was not associated with reclassification at confirmatory biopsy (odds ratio [OR]: 1.24, 95% confidence interval [CI]: 0.77–1.99). Among the remaining 603 men (median age: 63 years; follow-up: 60 months; 23% statin users), 149 (24%) had pathologic progression, while 200 (33%) had therapeutic progression. Statin exposure was not associated with pathological (multivariable hazard ratio [HR] 0.79, 95% CI: 0.51-1.23) or therapeutic progression (Continued on page 5)
Doc Moyad’s What Works & What is Worthless Column – Also Known as “No Bogus Science” Column
“The Final Verdict on Coffee is... You?”

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.

I am sick of reporting on coffee! It has been all over the news for so long you would think there was nothing more to report on this beloved beverage! Well, I was wrong because the subject of coffee keeps coming back again and again (kind of like the Star Wars franchise)!

Imagine a study that includes almost 500,000 participants that looks at total, ground, instant, decaffeinated coffee AND if that was not enough, it also takes into account how fast or slow a person metabolizes caffeine! Holy Number 2!

This observational study was just published, and it was known as “UK Biobank Study.” The average age of the participants was 57 years (range, 38-73 years), 46% were male, there were over 10 years of follow-up during this study and over 14,000 deaths occurred during this time. And, it seems coffee drinking (vs. non-coffee drinkers) was associated with a lower risk of dying earlier in life from all causes (including cardiovascular disease and cancer) and the benefits of coffee drinking were found for instant, ground and even decaffeinated coffee!

And, it did not matter if you were male or female or whether your body quickly or slowly metabolized coffee, it appears both types of metabolizers benefitted from drinking coffee. In fact, I hope you are sitting down for this, but even the group of participants consuming eight or more cups per day also appeared to get some health benefits! What the heck!? So, that whole every-thing in moderation is B.S.?

Well, here is my final verdict since I have been reporting on coffee studies for my entire diet career (33 or so years and counting) and the question will always remain, which is the following: “is it the coffee that makes people healthier, or do healthy people tend to gravitate toward coffee, making coffee appear healthier than it actually is, my friends?”

It appears from this massive study and others (in my opinion) that it is just as likely that healthier people tend to gravitate toward coffee. In other words, coffee is a major marker of a healthy lifestyle and healthy folks who drink coffee love to participate in some of these studies (aka fill out some of these questionnaires). I mean, within my own family and when I travel to Europe and other places, some of the healthiest folks I meet are also some of the most addicted coffee drinkers I have ever met, and they love to boast about their coffee drinking as much as their dog and/or kid’s accomplishments.

Anyway, does any of this matter anymore? No! In my opinion, whether it is the coffee or the drinker of the coffee, or a little of both, I believe if you love coffee you should drink it regardless of the science and if you hate coffee you should stay away from it regardless of the science. Some things in life are choice and what makes you happy should far outweigh what some “expert” thinks you should do. And, that being said, I need my daily Venti Latte from Starbucks because I just ran seven miles and I earned it!

Reference:
2. Moyad MA, 33+ years of doing the same thing.

DNA Test Identifies Increased Risk of Prostate Cancer (Continued from page 1)

The 1% of men at highest risk were 5.7 times more likely than the general population to develop prostate cancer – narrowing the absolute risk from around 1:11 to 1:2. The top 10% in the population risk distribution were 2.7 times more likely to develop the disease than the general population, corresponding to a risk of almost 1:4.

Interestingly, researchers found that many of the new genetic variants were found in the region of genes involved in communication between cells of the immune system and other cells. This implies that genetic errors in immune pathways may be affecting prostate cancer risk, and may have important implications for potential future treatment of prostate cancers with immunotherapies.

After this study, researchers believe that almost 30% of a man’s inherited risk of prostate cancer can be accounted for, which may be enough to start using the information in practical testing strategies. They plan to study a DNA test on saliva samples taken in general practices to evaluate whether advice or preventative treatment could reduce the number of cases of prostate cancer among those men found to have the highest inherited risk.

Ros Eeles, FMedSci, PhD, FRCP, FRCR, Professor of Oncogenetics at the ICR said, “By looking at the DNA code of tens of thousands of men in more depth than ever before... we have shown that information from more than 150 genetic variants can now be combined to provide a readout of a man’s inherited risk of prostate cancer.

“If we can tell from testing DNA how likely it is that a man will develop prostate cancer, the next step is to see if we can use that information to help prevent the disease. We now hope to begin a small study in GP practices to establish whether genetic testing using a simple spit test could select high-risk men who might benefit from interventions to identify the disease earlier or even reduce their risk.”

The content in this post has not been reviewed by The American Society Of Clinical Oncology (ASCO)® and does not necessarily reflect the ideas and opinions of ASCO.

The ASCO Post
21 June 2018
A biochemical assay identifying metastatic castration-resistant prostate cancer (mCPRC) best treated with androgen receptor signaling (ARS) inhibition or taxane-based chemotherapy for second- or later-line therapy has been validated in a multi-institution cohort study.

“Men testing negative for the androgen receptor splice variant 7 (AR-V7) protein in circulating tumor cells (CTCs) had a median survival of 19.8 months when treated with an ARS inhibitor (abiraterone or enzalutamide) vs. 12.8 months when treated with taxane-based chemotherapy such as docetaxel or cabazitaxel (Hazard Ratio [HR] 1.67, 95% Confidence Interval [CI] 1.00-2.81, P=0.05, a statistically significant difference),” stated Howard Scher, MD and colleagues of Memorial Sloan Kettering Cancer Center in New York City.

In contrast, median survival for AR-V7-positive patients who received taxane-based chemotherapy was longer, at 14.3 vs. 7.3 months with an ARS inhibitor (HR 0.62, 95% CI 0.28-1.39, P=0.25, not a statistically significant difference). The study was reported online in JAMA Oncology.

“These confirmatory findings will enable more informed and reliable therapy-guiding decisions for each man on the most appropriate treatments for his prostate cancer at critical decision points in management,” Scher said in a statement. “Armed with this knowledge, physicians and patients will feel more confident knowing that each individual is receiving the best treatment for them.”

Blood samples were obtained from a total of 142 men with mCPRC treated at Memorial Sloan Kettering Cancer Center, the Royal Marsden Hospital in England, and the London Health Sciences Centre in Canada. The study had an observational period of up to 4.3 years. The primary outcome of the study was overall survival (OS) after men received either class of agent as it related to their pretreatment AR-V7 status. The mean age of the group was 69.5 years, and approximately one-half were classified as high-risk based on conventional prognostic risk factors.

There were not enough low-risk patients who tested positive for AR-V7 to detect any survival differences between treatments.

However, among high-risk men, Scher’s group found that the nuclear-localized AR-V7 assay provided a more discriminating picture than it did for the group overall. In high-risk patients who tested negative for AR-V7, those on ARS inhibitors had better median OS than those on taxanes (16.9 vs. 9.7 months, HR 2.38, 95% CI 1.12-5.06, P=0.02, a statistically significant difference).

Conversely, high-risk AR-V7-positive patients who received an ARS inhibitor had a shorter median OS compared with those treated with a taxane (5.6 vs. 14.3 months, HR 0.35, 95% CI 0.14-0.88, P=0.03, a statistically significant difference).

“Thus, for patients classified as high risk by existing clinical biomarkers, a qualitative interaction exists, providing evidence of the treatment choice more likely to benefit men with both AR-V7-negative and AR-V7-positive test results in this group,” the investigators observed.

The main limitation to the study was that men were not prospectively randomized to treatment based on AR-V7 assay results. Nevertheless, the authors suggested that the test should still be considered for any patient where an improvement in OS is desired. “For patients with many comorbidities or who refuse a chemotherapeutic option, the AR-V7 test can still aid in patient management by identifying ARS inhibition-resistant disease for the purpose of directing patients to clinical trials or palliative care,” they concluded.

Metformin Added to Androgen Deprivation Therapy for Prostate Cancer Ups Survival

Metformin use is associated with prolonged survival among men with advanced prostate cancer receiving androgen deprivation therapy (ADT), according to a new study published online in The Journal of Urology. In a study of US veterans receiving ADT for advanced PCa, Kyle A. Richards, MD, of the University of Wisconsin in Madison, and collaborators found that patients also receiving metformin for diabetes mellitus had a significant 18% decreased risk of death compared with men who did not have diabetes mellitus (reference group). In addition, metformin users had a significant 18% decreased risk of skeletal-related events (SREs) and 30% decreased risk of cancer-related death.

“The current study is unique in evaluating the impact of metformin on ADT as these drugs may have an additive effect,” Dr. Richards and colleagues reported.

The study included 87,344 men, of whom 17% had diabetes mellitus being treated with metformin, 22% had diabetes mellitus not treated with metformin, and 61% did not have diabetes mellitus.

“Metformin activates AMP-activated protein kinase, which inhibits the mammalian target of rapamycin, a central regulator of cell growth,” the authors explained. In addition, ADT induces senescence in androgen-sensitive cells, a phenotype with high glycolysis and proteolytic turnover. Given these data, the investigators hypothesized that metformin used in combination with ADT may be beneficial in targeting PCa cells that persist after ADT, leading to improved survival.

Cancer Therapy Advisor
29 June 2018
Complications from Prostate Biopsy Detriment from Re-Biopsy

Men who experience a complication following transrectal ultrasound (TRUS)-guided prostate biopsy are less likely to comply with clinician requests for re-biopsy, new study findings suggest. Daniel Moreira, MD, MHS, of the University of Illinois at Chicago, and colleagues published results online in The Journal of Urology.

Of 4,939 men (aged 50 to 75 years) who underwent prostate biopsy at two years in the REDUCE trial, 5.3% experienced a complication such as hematuria, urinary tract infection (UTI), acute urinary retention (AUR), or hematospermia (blood in seminal fluid). In multivariable analysis, having any complication was associated with significant 65% greater odds of avoiding recommended re-biopsy at four years. Previous biopsy-related AUR, UTI, and hematospermia were associated with significant 4.5, 2.6, and 1.8 times greater odds of noncompliance, respectively. Results with hematuria were not significant.

“In men undergoing repeat prostate biopsy, a previous biopsy-related complication and the type of complication were associated with lower compliance with re-biopsy schemes,” stated Dr. Moreira. “Patients experiencing biopsy-related complications are ideal candidates to receive interventions regarding the importance of prostate re-biopsy to prevent noncompliance.” The investigators suggested urologists explain how the benefits of re-biopsy outweigh the risks. Whether these results apply to patients on active surveillance is unclear.

Prostate Cancer Advisor
15 June 2018

CDK12 Variants Make Tumors Vulnerable to Immune Checkpoint Inhibitors

Investigators from the U.S. and U.K. have identified a subtype of prostate cancer that may respond to immune checkpoint inhibitor drugs that are usually ineffective against prostate cancer.

This new tumor subtype is characterized by mutations in both copies of the gene cyclin dependent kinase 12 (CDK12) and the investigators suggested the possible future development of a genetic test to identify those men with this set of genetic changes who may benefit from immunotherapy.

Study results were published in the journal Cell (Vol. 173, pp. 1770-1782, 2018), and the study was conducted by investigators at the Institute of Cancer Research in London, U.K. and the University of Michigan in Ann Arbor, MI.

They analyzed DNA and RNA sequencing data collected internationally from 360 patients with metastatic castration-resistant prostate cancer (mCRPC), as well as data from 498 cases of primary prostate cancer in The Cancer Genome Atlas dataset. They detected aberrations of CDK12 in 25 of those 360 patients (6.9%) with mCRPC (95% CI 4.6% to 10.2%), a rate “significantly higher” than the 1.2% found in primary prostate cancer (6 out of 498 patients).

“Because prostate cancer is so common, 7% is a significant number,” said senior author Arul Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology, at the University of Michigan, in a news release coinciding with the study.

“That immune checkpoint inhibitors may be effective against this sub-type of prostate cancer makes it even more significant.”

Emmanuel S. Antonarakis, MBCh, associate professor of oncology and urology at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, who was not involved in the current study, noted in comments to MedPage Today, that while only about 10% of advanced prostate cancer patients respond to checkpoint inhibitor immunotherapy, “once achieved, these responses can be very durable, often lasting many years.

“Therefore, determining ahead of time which patients will respond favorably to these immune checkpoint agents is paramount to maximize benefit for patients and minimize futile treatment selection for those that won’t respond,” he said.

Chinnaiyan and colleagues noted that tumors with this genetic profile contain a higher number of immune cells than other forms of prostate cancer. Additionally, CDK12-mutated tumors have a higher number of protein fragments (neoantigens) on their surface that act as a red flag to the immune system.

Since tumors with a large number of immune cells and neoantigens are known to respond better to immunotherapy, Chinnaiyan and colleagues suggested it could explain why those men with CDK12 mutations benefit from immune checkpoint inhibitors, while other men with prostate cancer do not.

“These early clinical results support the hypothesis that metastatic prostate cancer patients who harbor biallelic CDK12 loss may have a higher likelihood of response to immunotherapy than an unselected metastatic prostate cancer population,” Chinnaiyan and his colleagues concluded, adding that identification of CDK12-mutation-associated neoantigens could help in the design of personalized tumor vaccines.

MedPage Today
19 June 2018

Statin Use (Continued from page 2)

In our study, statin use at diagnosis was not significantly protective against pathological or therapeutic progression in men undergoing AS for localized, low-risk prostate cancer.

Resources Address Anxiety, Depression and Prostate Cancer

Many men who are diagnosed with prostate cancer, or are managing the disease, experience some level of anxiety and/or depression. Caregivers may also be affected. The psychosocial challenges surrounding treatment choices and side effect management can have a negative impact on the prostate cancer journey. Anxiety and depression aren’t always effectively treated, in part because the symptoms may not be recognized.

We encourage you to visit the Us TOO web page for information on recognizing and managing anxiety, depression and prostate cancer.

www.ustoo.org/anxiety-and-depression
Finasteride Safely Prevents Prostate Cancer
“Those Results are Transformational,” Says Researcher

“Very long-term follow-up shows that finasteride is safe,” said Ian Thompson, MD in a press statement. He is professor emeritus at the University of Texas Health Science Center at San Antonio. “These results are transformational,” he explained. “We have found an inexpensive, effective drug that can prevent [prostate cancer].”

The new findings about prostate cancer (PCa) deaths, from the landmark Prostate Cancer Prevention Trial (PCPT), might seem incongruous at first.

After all, finasteride was so effective in reducing the risk for PCAs in that study that the placebo-controlled PCPT was stopped early and the results were published in 2003 in the New England Journal of Medicine.

But that is also when the troubles began, because the investigators simultaneously reported an increase in the number of high-grade cancers with the drug, compared with placebo (280 vs. 237).

“That finding tarnished finasteride,” said Thompson, who is principal investigator of the PCPT. “There is no question that the reason finasteride is not used for PCa prevention is because of the small but statistically significant increase in high-grade disease. Absolutely no question,” Thompson stated.

But new data address this old finding. If high-grade disease is more common with finasteride than with placebo, “there should be more PCa deaths [with finasteride],” he explained. But that’s not what the researchers found in their new analysis. Instead, there were fewer PCa deaths in the finasteride group than in the placebo group (42 vs. 56). The median follow-up was 18.4 years, and the cumulative follow-up was almost 300,000 patient years.

“We have no evidence that there’s an increase in prostate cancer death in the finasteride arm,” Thompson said. “In other words, the initial study findings about an increase in high-grade disease are not consequential. The new data took five years to gather,” he reported.

PCPT investigators matched more than 18,000 trial participants to the National Death Index, a centralized database of American death records. With this painstaking process, they were able to determine whether a trial participant had died and, if so, the cause of death.

“The lion’s share of this laborious work was performed by

(Continued on page 8)

Androgen Deprivation Therapy is Associated with Prolongation of QTc Interval (Part of Heart Rhythm) in Men with Prostate Cancer

Gagliano-Jucá T, Travison TG, Kantoff PW, et al.

J Endo Soc 2: 485-496, 2018

Context: Androgen deprivation therapy (ADT) for prostate cancer (PCa) is associated with increased cardiovascular mortality and sudden cardiac death, with some events occurring early after initiation of ADT. Testosterone levels are inversely associated with corrected QT (QTc) interval duration; therefore, prolongation of QTc duration could be responsible for some of these events during ADT.

Objective: To evaluate changes in QTc duration during ADT.

Design and Interventions: A six-month prospective cohort study that enrolled men with PCa about to undergo ADT (ADT group) and a control group of men who previously underwent prostatectomy for PCa and never received ADT (non-ADT group).

Patients: At study entry, all men were eugonadal (having normal testicular function) and had no history of cardiac arrhythmias or complete bundle branch block.

Outcomes: Difference in change in QTc duration from baseline on a 12-lead electrocardiogram (ECG) at six, 12, and 24 weeks after initiation of ADT vs. ECGs performed at the same intervals in the non-ADT group. PR, QS, and QT interval durations were also evaluated.

Results: There were 71 men in the study sample (33 ADT and 38 non-ADT). ADT was associated with prolongation of the QTc by 7.4 milliseconds (ms) compared with the non-ADT group [95% confidence interval (CI) 0.08 to 14.7 ms; P = 0.048, a statistically significant difference]. ADT was also associated with shortening of the QRS interval by 2.4 ms (95% CI -4.64 to -0.23; P = 0.031 a statistically significant difference). Electrolytes did not change.

Conclusions: Men undergoing ADT for PCa experienced a prolonged QTc. These findings might explain the increased risk of sudden cardiac death in these patients.

Enzalutamide

(Continued from page 1)

a smaller percentage of those in the enzalutamide cohort required these medications to begin with, compared with men in the placebo group (15% vs. 48%). Time to PSA progression was statistically significantly reduced for men who were given enzalutamide (37.2 months vs. 3.9 months, P=0.001).

While these data are encouraging, adverse events of grade 3 or greater were higher with enzalutamide vs. placebo (31% vs. 23%, respectively), which led to a higher frequency of trial discontinuation in the enzalutamide cohort. Two patient deaths in the enzalutamide arm were attributed to drug treatment. Other notable adverse effects observed in this cohort included hypertension, mental impairment, cardiovascular events, and falls, among others.

Three patients in the enzalutamide arm also had serious, drug-related convulsions, and five men receiving enzalutamide were identified as having “noninfectious encephalopathy or delirium.” Despite the appearance of these side effects, the authors concluded that there was “no decrease in quality of life associated with enzalutamide treatment.”

Cancer Therapy Advisor
29 June 2018

Keep up with the latest information on prostate cancer.
Be sure to follow Us TOO on Facebook:
www.facebook.com/UsTOOInternational
Doctor Chodak’s Bottom Line

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, “Enzalutamide...”
A major advance in treating advanced prostate cancer has been the development of enzalutamide. Given this benefit, it is logical that research has been underway using the drug earlier in the disease. One problem group is those with a rising PSA after local therapy for which no proven therapy improves survival. The study published in the New England Journal of Medicine found that the men receiving enzalutamide had a significantly longer time until developing metastatic disease. However, so far, there is no improvement in survival and some of the side effects are troubling. It is unclear whether the FDA will grant approval for the drug for this group of men based on results reported thus far. Nevertheless, it is an encouraging finding and hopefully we will learn more soon.

The Bottom Line: Enzalutamide used for a rising PSA after local therapy increases the time until developing metastases. More time is needed to understand its effect on survival, and until then, it remains experimental.

P1, Prostate Cancer...
Despite promising results from a Phase II trial of another immune stimulator called Prostvac-V/F, the results of a large, randomized trial failed to show any improvement in men with asymptomatic or minimally symptomatic castrate resistant prostate cancer. Prostvac is a vaccine that targeted PSA and previously had shown a survival benefit in a Phase II study. Sadly, as happens all too often, when tested more rigorously in a randomized fashion, it has not been effective. One interesting finding was that overall survival was about one year longer than had been anticipated and it raises questions whether, in a different population, the vaccine would have been effective. We do not know whether additional studies will be forthcoming.

The Bottom Line: The vaccine Prostvac was not able to improve survival in men with asymptomatic or minimally symptomatic castrate resistant prostate cancer.

P2, A Randomized Phase...
Many men with prostate cancer may sometimes find it hard to understand the results of some clinical trials. For example, if a drug is found to improve survival of men with metastatic disease, it would seem logical that the same drug should help men with less advanced disease. And yet, we get studies like the SPGC-13 trial, which randomized men with intermediate- or high-risk disease who received radiation and adjuvant androgen deprivation therapy to either six cycles of adjuvant docetaxel chemotherapy without prednisone or observation. After a median follow-up of nearly five years, there was no statistically significant difference in survival between groups. Could an explanation be that omitting the prednisone weakened the effect? For now it means that adding docetaxel after radiation is not worthwhile.

The Bottom Line: Adjuvant docetaxel does not improve survival of men with intermediate- or high-risk disease after treatment with radiation and androgen deprivation therapy.

P4, Metformin Added to...
Could diabetic men receiving metformin while also receiving androgen deprivation therapy have a side benefit? That is the suggestion by Richards and co-workers who conducted a large, retrospective review of veterans. They found that men on the drug had a significantly longer survival compared to either men without diabetes or those with diabetes but not taking metformin. Although interesting and potentially exciting, we have seen results with data like this many times before in uncontrolled studies, but when tested properly, the benefit is not sustained. Hopefully, these results will lead to a properly conducted randomized trial, but until then, it would not be appropriate for men without diabetes to consider getting this drug.

The Bottom Line: Metformin may be helpful for men on androgen deprivation therapy, but this needs to be properly studied before it is recommended to patients.

P5, Complications from...
Does getting a complication from a prostate biopsy influence a man’s decision to undergo a repeat biopsy? That appears to be the case based on the findings from the REDUCE trial, a study aimed at preventing prostate cancer using dutasteride. Men who had hematuria, urinary tract infection (UTI), acute urinary retention (AUR), or hematospermia (blood in seminal fluid) on their initial biopsy were significantly more likely to refuse a follow-up biopsy compared to men not having one of those complications. It is somewhat surprising that hematospermia and hematuria led to refusing a biopsy given their danger to the patient is so low. How these results will affect men on active surveillance, however, is unclear. In this trial, men were supposed to have a biopsy despite no suspicion of cancer, so it is easy to see

(Continued on page 8)
Phyllis Goodman, MS, a biostatistician at the Fred Hutchinson Cancer Research Center in Seattle, who is a member of the PCPT team,” Thompson noted. “With the latest data coming 25 years after the PCPT was started, we have answered the questions and closed the book.”

The trial was sponsored by the Southwest Oncology Group, and was designed to determine whether daily finasteride for seven years would prevent PCs in men older than 55 years.

The Bottom Line: A complication from a prostate biopsy could result in some men refusing a repeat biopsy.

P6, Androgen Deprivation...

Yet another side effect from androgen deprivation therapy appears to be the effect on QTc duration, which may become increased. This may partially explain why men on androgen deprivation therapy are at increased risk of cardiac mortality or sudden death from a cardiac event. Those are the findings from a small prospective study. If substantiated with more patients, the challenge will be to explore options that might lower this risk.

The Bottom Line: Androgen deprivation therapy may increase the QTc interval and contribute to the cardiac risk associated with this treatment, even in men without cardiac disease.