Abiraterone Acetate May Increase Risk of Mortality From CVD in Men with Prostate Cancer Hospitalizations Increased in All Abiraterone-Treated Patients

An increased risk of early death was observed in men with pre-existing cardiovascular disease (CVD) starting abiraterone acetate for advanced prostate cancer, a registry study found.

“Among abiraterone-treated men, increased mortality ranged from 21.4% for those with ischemic heart disease to 25.6% for those with acute myocardial infarction (MI), compared with 15.8% for those without a heart condition,” reported Grace Lu-Yao, PhD, MPH, of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia.

“Our data show that patients with existing cardiovascular conditions experience significantly higher 6-month mortality than those without CVD,” Lu-Yao said during a media briefing ahead of the American Association for Cancer Research (AACR) meeting, to be held March 29-April 3.

Of the 2,845 men in the study, 67.6% had a pre-existing heart condition (N=1,924). Patients with atrial fibrillation, congestive heart failure, and stroke had increased mortality risks of 24.4%, 23.4%, and 22.1%, respectively, within these first six months.

“Typically clinical trials exclude people who have significant medical problems,” said AACR President Elizabeth Jaffee, MD, of Johns Hopkins Medicine in Baltimore. “I think this is rationalized as a safety measure by both investigators and sponsors.”

In her presentation, Lu-Yao highlighted that roughly 40% of those without CVD, “Among abiraterone-treated men, increased mortality ranged from 21.4% for those with ischemic heart disease to 25.6% for those with acute myocardial infarction (MI), compared with 15.8% for those without a heart condition,” reported Grace Lu-Yao, PhD, MPH, of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia.

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Phase III Trial of PROSTVAC in Asymptomatic or Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer

gulley JL, Borre M, Vogelzang NJ, et al.
J Clin Oncol 28 February 2019; Epub

Purpose: PROSTVAC, a viral vector-based immunotherapy, prolonged median overall survival (OS) by 8.5 months vs. placebo in metastatic castration-resistant prostate cancer (mCRPC) in a phase II study. This phase III study was intended to further investigate those findings.

Patients and Methods: Patients were randomly assigned to PROSTVAC (Arm V; N=432), PROSTVAC plus granulocyte-macrophage colony-stimulating factor (Arm VG; N=432), or placebo (Arm P; N=433), stratified by serum PSA (<50 vs. ≥50 ng/mL) and lactate dehydrogenase (<200 vs. ≥200 U/L). Primary end point was OS. Secondary end points were patients alive without events (AWE) – namely, radiographic progression, pain progression, chemotherapy initiation, or death – at six months and safety. The study design was a superiority trial of PROSTVAC (Arm V or Arm VG) vs. Arm P. Three interim analyses were planned.

Results: At the third interim analysis, criteria for futility were met and the trial was stopped early. Neither active treatment had an effect on median OS (Arm V, 34.4 months; hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.84 to 1.20; P=0.47; Arm VG, 33.2 months; HR, 1.02; 95% CI, 0.86 to 1.22; P=0.59; Arm P, 34.3 months). Likewise, AWE at six months was similar (Arm V, 29.4%; odds ratio, 0.96; 95% CI, 0.71 to 1.29; Arm VG, 28.0%; odds ratio, 0.89; 95% CI, 0.66 to 1.20; placebo, 30.3%). Adverse events were similar for the treatment and placebo groups, with the most common being injection site reactions (62% to 72%) and fatigue (21% to 24%). Arrhythmias (irregular heart beat) were the most common cardiac-related events (1.4% to 3.5%). No cases of myocarditis or pericarditis were reported. Serious treatment-related events occurred in <1% of all patients.

Conclusion: Whereas PROSTVAC was safe and well tolerated, it had no effect on OS or AWE in mCRPC. Combination therapy is now being explored in clinical trials.

Stereotactic Body Radiotherapy Shows Long-Term Safety in Prostate Cancer

Stereotactic body radiotherapy (SBRT) appears to provide good long-term results and few toxic effects in certain prostate cancer (PCa) tumors, according to data from thousands of patients. Researchers examined data from 2,142 men who underwent SBRT from 2000-2012. Doses ranged from 33.5 to 40.0 Gy in four to five fractions. SBRT was delivered on consecutive days, every other day, or once a week. Overall, 55.3% of men had low-risk, 32.3% had favorable intermediate-risk, and 12.4% had unfavorable intermediate-risk PCa. Median follow-up was 6.9 years.

At seven years, cumulative rates of biochemical recurrence were 4.5% for low-risk disease and 10.2% for all intermediate-risk disease (8.6 and 14.9% for favorable and unfavorable intermediate-risk disease, respectively). Severe toxic events were rare, with a seven-year cumulative incidence of late grade 3 or higher genitourinary (2.4%) and gastrointestinal (0.4%) toxic events. “This study presents long-term outcomes data indicating that a short course of RT, using a higher dose per day, has a highly favorable efficacy and side effect profile for low- and intermediate-risk PCa,” stated Dr. Amar U. Kishan of the University of California, Los Angeles.

Dr. Kishan concluded, “This approach significantly minimizes the burden of treatment and provides a very convenient alternative to other forms of treatment for this very common disease.” Dr. Rahul Tendulkar, a radiation oncologist at the Cleveland Clinic, in Ohio, told Reuters Health by email that the series “is the largest pooled study of SBRT for early-stage prostate cancer in the medical literature to date. It adds robust validity to the observations that prostate SBRT is well tolerated with very few toxic events, has excellent tumor control, and is more convenient for patients than many other treatment options.”

“While we await ongoing randomized trials directly comparing prostate SBRT to conventionally fractionated or hypofractionated radiotherapy regimens, the current data suggest that carefully performed prostate SBRT is an effective treatment option that can and should be discussed with most patients with early stage prostate cancer,” said Dr. Tendulkar, who was not involved in the research.

Reuters Health
16 February 2019
Doc Moyad’s What Works & What is Worthless Column — Also Known as "No Bogus Science" Column
“The Secret to Our Dog’s Long Life is_______?”

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.

We have a little dog — and boy, do I love this little guy (most of the time except when he begged me to take him for a walk outside this winter to go number 2 when it was exactly minus 17 degrees... aka “free cryosurgery treatment day” whether you like it or not. He (Chauncey) still looks so young at 14 years of age that the kids all around the block and some adults point to him and yell out “puppy!” So, Dr. Moyad have you been drinking? What are you talking about? I am talking about the fact that our dog should not be living this long and simultaneously in such great shape. What the heck is going on? Our veterinarian just shakes her head every visit and is amazed how he hasn’t gained weight in all of his adult years.

What is his secret? Moyad magic? Nope, I constantly feed him human food under the table when no one is looking because I do whatever it takes to have him pay attention to me for just a second, instead of my wife (he has always liked her the most). Is he taking some kind of anti-aging hormone or has he had some kind of doggy plastic surgery or Botox to give him the impression that he is young? I am convinced I know the answer and so does our doggy doctor. Our dog is a strange dog because for his entire life he aggressively demands to go to the bathroom FAR from the house twice a day, every day, and 365 days a year. He will not go in the yard or anywhere near the house. I am not kidding, I have never seen anything like it! You see we live in an age of obesity, not just for humans, but dogs and other pets. And, this brings me to the study of the month that received little-to-no attention, but I thought it was truly amazing. A North American study of over 50,000 client-owned dogs that attended approximately 900 veterinary hospitals was just published. IN ALL BREEDS they studied, they found that that a normal body weight was strongly associated with a lower risk of death compared to the overweight dogs (especially from midlife onward). This was such a consistent finding that I could not help but report it as yet another reason to be active and do what you can to maintain a healthy weight or waist. Male dogs also have a prostate, so we also share that interesting anatomical bond. Another study at the end of 2018, which was of U.S. adult humans, found that over 25% of people sit more than eight hours a day and almost 45% report being inactive. So, now you at least know my dog’s secret. He has figured it out. He gets his owners to walk him twice a day for his entire life so he can live as long as possible. Oh, and did I also tell you he is the happiest dog I have ever met? No kidding! Gee, I wonder if his mood is related to his regular physical activity?! Okay, that was rhetorical and that was sarcasm! Find me a pill that gives you that magical two-for-one (mental and physical health) and I will give you a Nobel doggy treat (aka “prize”).

References:
2. Ussery EN, Fulton JE, Galuska DA, et al. JAMA 320: 2036-

Radiological Agent Shows Promise in Heavily Treated mCRPC

PSA Decline of 50% or Greater in Two-Thirds of Patients

A novel, targeted radionuclide therapy showed promising activity for men with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC), the phase II LuPSMA trial found.

“Overall survival (OS) was 13.3 months (95% confidence interval [CI] 10.5-18.0 months) among 50 men with prostate-specific membrane antigen (PSMA)-positive mCRPC receiving lutetium-177 PSMA-617 (\textsuperscript{177}Lu-PSMA-617),” reported Michael Hofman, MBBS, of the Peter MacCallum Cancer Centre in Melbourne, Australia.

While my strong impression is that this is a life-prolonging therapy, this is not a claim that we can make yet, because there’s no comparator arm,” Hofman said during a press briefing ahead of the 2019 Genitourinary Cancer Symposium (GUCS).

High response rates and low toxicity were seen with treatment, and he noted that the survival data in the single-arm study compared favorably to historical averages of nine months for this group. In prostate tumors, PSMA expression is 100 to 1,000 greater than in normal tissue, with expression further increased in men with mCRPC. PSMA-617 is a small molecule that binds to PSMA, and with \textsuperscript{177}Lu attached, delivers beta-radiation directly to tumor cells.

In the LuPSMA trial, the investigators “personalized” the therapy by conducting a PET scan in each participant prior to treatment to ensure their disease sufficiently expressed PSMA and would therefore be more likely to respond to \textsuperscript{177}Lu-PSMA-617. In all, 74% of men had a PSA decline of ≥30%, 64% had a PSA decline of ≥50%, and 44% had a PSA decline of ≥80%. Median OS was 18.0 months for the 37 men with a PSA decline ≥50% vs. 8.7

(Continued on page 6)

Video is Available from:

Prostate Cancer Pathways for Patients and Caregivers Webcast

With Content Specific to:
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Access direct links to video pertaining to each specific topic at: https://ustoo.org/Pathways-EnglewoodNJ
two treatments decreasing held among men with intermediate-risk disease.

“Increasing AS over time is encouraging,” said lead author Brandon A. Mahal, MD, a radiation oncologist at the Dana-Farber Cancer Institute in Boston, MA. This “suggests that clinicians are better adhering to current recommendations and guidelines, and this will reduce overtreatment,” he said.

However, another expert was surprised that the reported numbers were so low. “Despite these positive trends, it is concerning that, as of 2015, still only 42% of low-risk men were being managed conservatively,” said Stacy Loeb, MD, a urologist at NYU Langone Health in New York City, in an email to Medscape Medical News.

Loeb and colleagues recently reported much higher rates: 72% of men <65 and 79% of men ≥65 years or older with low-risk PCa seen in the US Department of Veterans Affairs (VA) Health System were managed conservatively through 2015. How could two studies from the U.S. have such different findings? “The data sources — and what they reflect in terms of treatment settings — could be the explanation,” said both Mahal and Loeb.

The new findings are derived from the SEER Prostate Active Surveillance database. These men were managed in a variety of settings. On the other hand, Loeb’s VA study is from just one healthcare system.

Mahal also pointed out that the VA study included a proxy for AS via administrative codes, but not a validated AS variable, which was embedded in the custom SEER database. Still, Loeb pressed her point that the newly reported rate of AS is still low — given what can be achieved.

Other findings reinforce her argument. For example, data from the National Prostate Cancer Registry of Sweden showed that 74% of men with low-risk PCa there were managed with AS in 2014.

Mahal and colleagues, most of whom are also radiation oncologists from Boston institutions, also highlight another trend that emerged from 2010 to 2015 in the U.S., for men with higher-risk PCa, management patterns shifted toward more use of RP and away from the use of RT.

This shift “does not coincide with any new level 1 evidence or guideline changes,” they point out. The rate of surgery increased by 5% for high-risk PCa, while the rate of RT declined by 5%.

“This ‘downstream effect’ of AS on RP, performed by urologists and RT, performed by radiation oncologists, needs further examination,” the authors state. “This finding is provocative and may be a focal point of debate,” said Mahal in a press statement. “Further studies will be needed to determine whether this trend continues and what forces may be driving this trend,” he added.

The authors end their letter by observing that the study only investigated initial management patterns. How the trends will translate into clinical outcomes is unknown, they conclude.

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Medscape Medical News
11 February 2019

Abiraterone Acetate & Increased CVD Mortality

(Continued from page 1)

prostate cancer patients have uncontrolled hypertension. These men, plus those with a history of major heart conditions, are usually excluded from clinical trials. In the STAMPEDE study, for example, exclusion criteria included men with a history of severe angina or heart failure, and those with a recent MI.

Jaffe noted that testing new agents in the healthiest men does not provide the real-world data physicians need.

The researchers used Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data to look at prostate cancer patients treated with abiraterone from 2011 to 2014.

The study also found an increased risk of hospitalizations by examining hospital use in the 6 months before and after starting abiraterone treatment. Risk of hospitalization was increased for patients without a history of CVD for incidence rate ratios (IRR) 1.43 (95% CI 1.30-1.57), as well as for those with pre-existing CVD:

- Acute MI: IRR 1.44 (95% CI 1.12-1.86)
- Congestive heart failure: IRR 1.35 (95% CI 1.21-1.51)
- Stroke: IRR 1.30 (95% CI 1.07-1.57)
- Atrial fibrillation: IRR 1.27 (95% CI 1.09-1.48)
- Ischemic heart disease: IRR 1.22 (95% CI 1.01-1.48)

The study captured the period from when abiraterone was first approved by the FDA in 2011 for use in late-stage castration-resistant prostate cancer after prior treatment with docetaxel, and when it was then expanded in 2012 to also include use before chemotherapy.

In the study, roughly 20% of the patients had received prior chemotherapy (N=586), with the rest being chemotherapy naive. Lu-Yao said that regardless of prior chemotherapy use, the patterns for both early mortality and hospitalization were “quite similar.”

Jaffe noted that the study is retrospective, but still provides important data, similar to that of a phase IV study.

“One a drug’s approved, all physicians can administer these drugs, and we don’t really have a handle on who may have worse side effects from these drugs,” she said. “We know that all therapies have side effects, and we need to be able to predict early, screen early, so we can at least monitor for these side effects and intervene at an early stage before patients have severe consequences from these drugs.”

Study limitations included the possibility of misclassification of patients’ CVD, the fact that treatment efficacy could not be assessed, and that there was no control group to look at expected survival for this patient population. A lack of clinical data also meant that the researchers could not compare the study population against the pivotal trials of abiraterone acetate.

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7 February 2019

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Enzalutamide Plus ADT Boosts Outcomes in Advanced Prostate Cancer

Enzalutamide has already demonstrated a benefit in men with metastatic and nonmetastatic castration-resistant prostate cancer (mCRPC), but its efficacy when combined with androgen deprivation therapy (ADT) has, until now, been unclear. Results from the phase 3 ARCHES trial presented at the 2019 Genitourinary Cancers Symposium (GUCS) show that enzalutamide added onto ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC) significantly extended radiographic progression-free survival (rPFS), and that benefit (observed across all prespecified endpoints) improved outcomes, as compared with ADT alone.

Andrew Armstrong, MD, professor of Medicine, Surgery, Pharmacology and Cancer Biology, and director of research in the Duke Cancer Institute’s Center for Prostate and Urologic Cancers, in Durham, NC was lead author. ARCHES included men with both low- and high-volume disease and with and without prior docetaxel therapy. Overall, 1,150 men were randomized to receive either ADT plus enzalutamide 160 mg/day (N=574) or ADT plus placebo (N=576). Men were stratified by disease volume and prior docetaxel therapy. At the time of data cut-off, 769 men remained on treatment, 437 (76%) for enzalutamide and 332 (56%) for ADT alone. Median follow up was 14.4 months. At data cutoff, 262 events of radiographic progression (77 vs. 185 in the combination and ADT groups, respectively) were reported. There were also 25 deaths without radiographic progression. The median time to rPFS event was not reached in the combination group and 19.4 months in the ADT alone group (hazard ratio [HR], 0.39; P <0.0001).

Significant improvements in rPFS were also observed in all prespecified subgroups, including disease volume, pattern of disease localization at baseline, geographic region, and prior docetaxel use (HRs 0.24-0.53).

Enzalutamide plus ADT was also superior to ADT alone when looking at the secondary endpoints. The combination reduced risks of PSA progression and starting a new antineoplastic therapy. Median time to castration resistance was not reached in the combination group vs. 13.9 months for ADT alone (HR, 0.28; P <0.0001).

Undetectable PSA and objective response rates were also significantly higher (68.1 vs. 17.6 and 83.1 vs. 63.7%, respectively, both P <0.0001).

“The risk of radiographic progression or death was reduced by 61% vs. ADT alone,” said Armstrong. “The significant benefit in rPFS was seen in all prespecified subgroups, including low- and high-volume disease in men with or without prior docetaxel therapy.”

Armstrong noted that adverse events were generally consistent with those reported in other enzalutamide clinical trials. Grade 3 or 4 events were reported in 23.6% receiving enzalutamide vs. 24.7% for ADT alone. The most common events reported in the combination group included hot flashes, fatigue, arthralgia, hypertension, nausea, musculoskeletal pain, diarrhea, asthenia, and dizziness.

“Analysis of quality of life is ongoing and will be presented at future meetings,” said Armstrong. “These men were generally asymptomatic and had a high quality of life.”

(Continued on page 8)
Radiological Agent
(Continued from page 3)

Minimal Benefit of Aspirin Use Post-Prostate Cancer Diagnosis
Disease Mortality Risk Reduced in Low-Grade Cancer & More When Used Longer Than Five Years

Synopsis and Perspective:

Use of low-dose aspirin after a PCa diagnosis did not appear to reduce overall disease mortality at five years, according to a new nationwide Danish registry study. In this large-scale cohort study, researchers conducting a multivariable analysis found no significant overall difference in PCa-specific mortality between aspirin and non-aspirin users at a median follow-up of 4.9 years (Hazard Ratio [HR] 0.95, 95% confidence interval [CI] 0.89-1.01), Charlotte Skriver, MSc, of the Danish Cancer Society in Copenhagen, and colleagues reported online ahead of print in the *Annals of Internal Medicine*. However, Skriver’s team discovered that in men with the least aggressive type of disease (Gleason score ≤6), low-dose aspirin was associated with a reduction in PCa-specific mortality (HR 0.82, 95% CI 0.70-0.97).

Researchers saw the most pronounced effect in a secondary analysis at 7.5 years. Low-dose aspirin use was associated with a 16% reduction in the risk of PCa death (HR 0.84, 95% CI 0.72-0.97). Men who took more than 1,096 tablets (HR 0.77, 95% CI 0.65-0.91) during this time, or for more than 1,096 days (HR 0.79, 95% CI 0.67-0.93) appeared to derive the most benefit.

“The study did not support an overall effect of post-diagnosis low-dose aspirin use on PCa mortality,” they wrote. “However, results for extended exposure periods suggest that low-dose aspirin use might be inversely associated with prostate cancer mortality after five years from cancer diagnosis.” To conduct their study, Skriver and colleagues selected men in Denmark diagnosed with PCa from 2000 to 2011 whom they identified from the Danish Cancer Registry. Researchers obtained mortality data from the Danish Registry of Causes of Death.

Low-dose aspirin was defined as 75, 100, or 150 mg per tablet. Notably, almost all low-dose aspirin in Denmark is prescription aspirin, the researchers explained. Users were defined as men who had two or more prescriptions following their PCa diagnosis, while non-users were defined as men who filled fewer than two prescriptions.

The study consisted of 29,136 men with PCa, median age 70 years, 7,633 of whom died of PCa and 5,575 of whom died of other causes during a median follow-up of 4.9 years (interquartile range, 3.1 to 7.2 years), through 2015. Post-diagnosis low-dose aspirin use was associated with adjusted hazard ratios of 0.95 (95% CI 0.89-1.01) for PCa-specific mortality and 1.12 (95% CI 1.05-1.20) for other-cause mortality. Secondary analyses showed that PCa mortality was slightly reduced with low-dose aspirin after the five-year (HR 0.91, 95% CI 0.83-1.01) and 7.5-year (HR 0.84, 95% CI 0.72-0.97) post-diagnosis exposure periods, notably among men filling prescriptions for a large quantity of low-dose aspirin tablets during the 7.5-year period.

“Beyond this study, to date, research on regular-dose aspirin and PCa survival has been inconclusive,” the authors wrote. “Regarding its possible mechanism of action in PCa, aspirin is known to induce apoptosis, and to reduce cell growth and invasion in the prostate tumor,” they noted. It is a known inhibitor of the cyclooxygenase (COX) enzymes, which has anti-cancer effects. While they note that COX-2 overexpression has been seen in PCa tumors and is associated with poor prognosis, aspirin at low doses mainly inhibits both COX-1 and platelet function. “But increasing evidence indicates that its antiplatelet effect influences COX-2 activity and is involved in cancer cell dissemination and metastasis,” they wrote.

This study’s strengths include the large-scale population characteristic of a comprehensive national registry with many details of the population. Limitations include confounding, as low-dose aspirin is mainly used for cardiovascular protection, therefore cardiovascular mortality competed with prostate cancer death in this study; participants who took low-dose aspirin might have been at greater risk for death from cardiovascular causes. Another potential confounding factor was a lack of data on lifestyle factors such as body mass index and smoking, both of which would have increased the risk of death from cardiovascular disease. In addition, for 27% of participants, information was missing on the clinical stage of their cancer, Gleason scores, and nonsurgical PCa therapies.

Reference:

Ann Intern Med, 2019; DOI: 10.7326/M17-3085

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8 March 2019

US TOO INTERNATIONAL PROSTATE CANCER EDUCATION & SUPPORT

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Hot SHEET – APRIL 2019

Men responded again with a median follow-up of 4.9 years for those with a decline of <50% (P=0.001). Hofman explained that 20-30% of all mCRPC patients overexpress PSMA to a level that would make them eligible for treatment.

Two phase III trials, followed one of which is testing 177 Lu-PSMA-617 vs. cabazitaxel while the other – the VISION trial – is testing the agent against best standard of care.

“This is a very intriguing agent, and the VISION study is open in the U.S., which is a registration trial,” said moderator Robert Dreicer, MD, of the University of Virginia in Charlottesville and an American Society of Clinical Oncology-designated expert.

The current study enrolled 50 men, with a median age of 71. Prior therapies included abiraterone, enzalutamide, or both in 90%; docetaxel in 84%; and cabazitaxel in 48%. Hofman stated that, “All men really had quite aggressive disease as evidenced by the PSA doubling time,” (PSADT = 2.6 months).

Men received a median of four treatment cycles, with eight stopping early due to “exceptional response” and 10 due to disease progression. Retreatment with Lu-PSMA-617 seemed feasible. In 14 men who had initially responded but later progressed, treatment was re-administered; nine of these men responded again with a PSA decline of ≥50%.

Common adverse events reported in prior 177 Lu-PSMA-617 studies were grade 1 dry mouth, grade 1/2 transient nausea and fatigue, and possible drug-associated Grade 3/4 thrombocytopenia.

Presented at the 2019 GUCS, abstract 228

MedPage Today
12 February 2019
P1, “Active Surveillance…” My, how things are changing in managing localized prostate cancer (PCa)! Quite appropriately, an increased percentage of men with low-risk disease are not getting immediate therapy. Rather they are going on active surveillance (AS). Mahal and co-workers analyzed data from SEER and between 2010 and 2015 found an increase in the percentage of men selecting observation from 15% to 42%. Although an important trend, to many clinicians that number is far too low. The question is, why isn’t it higher? One explanation may be that men are not receiving the appropriate information about the results with AS. As I have often stated, standardizing the information men receive about their options for local therapy is necessary to avoid bias. Another possibility is that the percentage has continued to increase and will be evident when more recent data become available.

The Bottom Line: The percentage of men choosing AS is increasing the U.S. but, at least as of 2015, too many men were still getting definitive treatment.

P1, “Abiraterone Acetate…” Abiraterone acetate has been shown in randomized trials to offer a significant benefit for men with advanced PCa with a relatively low incidence of side effects. However, a retrospective analysis by Lu-Yao and co-workers found a high incidence of cardiovascular mortality within six months of beginning therapy among men with a pre-existing heart condition. That was not seen in at least one of the large randomized studies evaluating abiraterone (https://www.nejm.org/doi/full/10.1056/nejmoa1014618). This may be explained, in part, by the fact that men with significant cardiovascular disease were excluded from the study. The new study also found an increased risk of hospitalization among these men. Clearly this information is important to present to new men with cardiovascular disease before they go on abiraterone plus prednisone.

The Bottom Line: Abiraterone plus prednisone may be associated with a significant risk of dying from a cardiovascular event if men have a history of significant cardiovascular disease.

P1, “Another Win in…” Another new androgen receptor inhibitor is likely to get approved to help men with non-metastatic castrate resistant prostate cancer (CRPC). Darolutamide was compared to placebo and found to more than double the time to median metastasis-free survival. However, the drug’s approval is occurring without proof that overall survival is also improved so more data will be needed to understand its effect compared to other treatment options. Median survival has not yet been reached but, thus far, there is about a 10% lower mortality in the darolutamide group.

The Bottom Line: Encouraging results show a benefit of darolutamide in men with non-metastatic CRPC but an overall survival benefit has not yet been achieved.

P2, “Phase III Trial of…” Previous results with Provenge, an immunotherapy, showed an improvement in survival in men with progressive metastatic PCa. A newer immunotherapy called Prostvac has also shown promise in phase II studies, including overall survival. However the results of a new phase III randomized study have failed to show a benefit. Men were randomized to Prostvac alone, Prostvac plus granulocyte macrophage colony stimulating factor or placebo. No significant difference in overall survival was found among the three treatment groups. These results were unexpected given the previous phase II findings and again demonstrated why overall survival must be assessed in a phase III trial to know if a treatment truly offers patients a significant benefit.

The Bottom Line: Prostvac immunotherapy has failed to show a survival benefit in men with progressive metastatic disease, but it will be tested in other groups of men.

P2, “Stereotactic RT…” Data continue to accumulate using stereotactic radiotherapy (RT) although long-term survival data are still lacking. In the latest study, morbidity continued to remain low with grade III GU events of only 2.4% and grade III GI events only 0.4%. Clearly this tissue is more convenient for men and, with a low morbidity, it is likely to become a treatment of choice providing the survival data is comparable to conventional RT. Hopefully survival results will be available soon.

The Bottom Line: Stereotactic body RT shows a low toxicity profile and hopefully survival will at least be comparable to conventional RT.

P5, “Enzalutamide Plus…” Enzalutamide has been shown to improve survival in men with progressive metastatic PCa. Data from a large randomized study has now shown that adding this drug to androgen deprivation therapy (ADT) men with newly diagnosed hormone sensitive metastatic PCa can significantly improve outcomes compared to ADT alone. Armstrong, et al. found that radiographic progression free survival (rPFS) was significantly prolonged. The median time to rPFS median time to rPFS event was not reached in the combination group but it was only 19.4 months in the ADT alone group (hazard ratio [HR], 0.39; P <0.0001). More time is needed to see that this benefit translates into a survival benefit. The benefit occurred without a significantly higher incidence of severe side effects.

The Bottom Line: Newly diagnosed men with metastatic disease have significantly better outcomes when enzalutamide is added to ADT compared to ADT plus placebo and it is likely to become the new standard of care.

P6, “Minimal Benefit of…” Aspirin or no aspirin for men diagnosed with prostate cancer? Data from a large observational study in Denmark found no benefit to men, except for those with Gleason score <7 cancers. Other studies have failed to show a (Continued on page 8)
Enzalutamide Plus ADT vs. ADT (Continued from page 5)

Commenting on the study, Bobby Liaw, MD, clinical director of genitourinary oncology at Mount Sinai Health System in New York City, who was not involved with the current research, put the new results into context. In recent years, “clinical trials have demonstrated the clinical benefits of the addition of docetaxel or abiraterone, which had both previously been reserved for the mCRPC setting, to standard-of-care ADT for the treatment of mHSPC. The phase 3 ARCHES study continues this trend by showcasing that the combination of enzalutamide plus ADT demonstrates a significantly improved radiographic progression-free survival benefit vs. ADT alone. “As more highly active therapeutic agents find their way into the mHSPC space, optimal drug selection and sequencing will be a growing issue,” noted Liaw. He cautioned, however, that there is no definitive study data available yet to provide clear guidance.

“Additional follow up of the ARCHES study cohort may start to shed some light on this clinical question, as 18% of enrolled patients had received prior docetaxel as part of their mHSPC management,” he added.

Ian D. Davis, MBBS, PhD, FRACP, FACHPM, Monash University Eastern Health Clinical School, Australia, who served as study discussant at the meeting, pointed out that overall survival data is not yet available, and that it is yet unknown if the treatment is cost effective. He suggested, “cautiously, this should probably not yet change practice.”

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The Bottom Line (Continued from page 7)

clear benefit but no randomized studies have been done. The challenges of evaluating this kind of study are numerous. For example, it is hard to validate the exact usage and dosage and, of course, the men may have other variables not standardized. Do the data support the need for a prospective study? Probably yes, but it seems unlikely that it will occur.

The Bottom Line: Routine use of aspirin does not clearly benefit men with newly diagnosed PCAs, but it might help men with lower-risk disease. However, that would require a randomized study to test properly.

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 important information on recognizing and managing anxiety, depression and prostate cancer.

www.ustoo.org/anxiety-and-depression
QUESTION FROM PROSTATE CANCER SURVIVOR:
I like this new Between the Sheets feature. In 2008, I had radiation seeds implanted. My PSA has been near 0 since then. Until about six months ago, using the pump produced acceptable length and hardness. Since then, at age 79, there is usually insufficient length and hardness. Question: Should I expect the same effects as RP (radical prostatectomy) surgery as described in the Jan 2019 Between the Sheets? I am just about ready to begin “the pill.” Any extra effects from the pill that I should be aware of?

RESPONSE FROM DR. JEFFREY ALBAUGH:
Thank you for your support for the column and for your question. I would not expect you to have the same issues with orgasm as described after radical prostatectomy this many years (more than a decade) after your radiation therapy. It is interesting that you have had pretty good results using the vacuum device for erections and length until six months ago. Make sure your vacuum device is still working properly to produce the suction needed to pull the blood in your penis. The device can stop working completely or partially and maybe you need a new device (especially if it is the original one you have been using for over 10 years). We do sometimes have men use the vacuum device daily for stretching the tissue and blood filling without the tension ring beginning about a month after the radical prostatectomy surgery. This may be helpful with preserving/restoring length when used in that early post operative period, as suggested from a few small research studies. The recommendation is to have men use the device daily for about 10-20 minutes for stretching without the ring. The goal is to create a painless, even erection that lifts off the cylinder within the device for about 1-2 minutes each time, repeating the sequence 5-10 times. Work with the device during each sequence doing multiple releases and adjustments, as needed (releasing each time it is hurting at all, if it is getting fatter at the base, or pulling in other tissue), until the penis lifts off the cylinder within the device. It can be helpful to work with an expert on the pump to learn to get these even, painless, lifted off erections. Sometimes the expert may be a representative from the vacuum device company or a healthcare professional (for example a nurse or medical assistant).

If you can get any fullness or hardness with stimulation, it is very helpful to start with that, rather than when completely flaccid. Many men who find some benefit from the pills will use the pills to get a better erection along with the vacuum device. The pills are taken on an empty stomach about 1-2 hours prior to stimulation and using the vacuum device. It is really helpful to start with any penile fullness or hardness that you can get. If you get harder with the pills, you can put that semi-hard or full penis in the pump, and it already has some more blood in there and will usually fill that much easier with the vacuum device. Many men have minimal side effects from the pills (sildenafil, vardenafil, tadalafil and avanafil). The most common are typically headache, nasal stuffiness, facial flushing and stomach upset. Some people get blue halos around lights with sildenafil or muscle aches with tadalafil. Very few people stop the pills related to intolerable side effects, but everyone is different, so it is difficult to say if you will have any unwanted side effects. I hope it goes well and you have minimal to no side effects with a positive effect on your erections. Remember to take the pill on an empty stomach (1 hour prior to or 2 hours after a meal). The peak effect of sildenafil, vardenafil and tadalafil usually takes about 60-90 minutes after taking it on an empty stomach. Remember, generic versions of sildenafil and tadalafil are now available and can be much less expensive.

You can access the new edition of my book or download a free copy of my original book at www.drijeffalbaugh.com.

Watch Dr. Albaugh’s presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at NorthShore University HealthSystem in Skokie, IL on November 3, 2018 at https://www.youtube.com/watch?v=HiqOdBEB110&t=4483s.

Read previous issues of Between the Sheets at www.ustoo.org/BTS.

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to:  uestooBTS@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
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Des Plaines, IL 0018
Progress on Prostate Cancer Research

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man’s prostate cancer and maximize his quality of life. Us TOO is excited to introduce this new, regular Hot SHEET supplement which includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than $745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

Racial Disparities in Prostate Cancer Treatment and Outcomes: Biology or Access to Care

An ongoing challenge in the prostate cancer community is the recognition that African American men have significantly higher prostate cancer incidence and mortality rates compared with Caucasian men, and are typically diagnosed at a younger age with more aggressive disease. Understanding the reasons for these disparities is critical for improving outcomes for African American men.

National Minority Health Month is observed every year in April to call attention to the health disparities that persist among racial and ethnic minority populations and the ways in which society can help advance health equality.

The Prostate Cancer Foundation would like to highlight a recent research study published in the Journal of Clinical Oncology (https://ascopubs.org/doi/abs/10.1200/JCO.18.01279) addressing these issues. Of course, research and other efforts to close these gaps do not stop when the month is over – our investigators continue their work throughout the year to measure, intervene, and advocate for patients.

Differences in Clinical Outcomes Between Black and White Men with Metastatic Castration-Resistant Prostate Cancer

To identify factors influencing disparities, PCF-funded researcher Dr. Susan Halabi of Duke University investigated overall survival outcomes of African American versus Caucasian men with metastatic castration-resistant prostate cancer (mCRPC) in randomized phase III clinical trials testing the efficacy of docetaxel or docetaxel-containing regimens. Nine phase III trials with outcomes for 8,028 patients were used in this meta-analysis (an analysis that combines many similar studies to increase the statistical power). Of these patients, 85% self-identified as Caucasian and 6% as African American.

Despite some differences in baseline characteristics, African American men and Caucasian men had similar median overall survival (time from randomization on the trial to death from any cause) across all of the trials, of 21 months. Progression-free survival (time from randomization to disease progression or death, whichever occurred first) was also similar in African American men and Caucasian men on these trials, with a median of 8 months for both.

However, when differences in important prognostic characteristics (such as age, performance status, PSA, and site of metastases) were statistically adjusted for, African American men had 19% lower risk for death than Caucasian men. Readers should note that these results are from clinical trials, and may not be generalized to the U.S. population.

These results suggest that when treatment is similar, disparities are not observed, and support hypotheses that disparities result from unequal access to care. Unequal access to health care for African Americans is a problem that has been well-documented in medical literature. At the same time, differences in biology may contribute to African American men being diagnosed at higher rates, at younger ages, and with more aggressive disease, and may affect treatment responses.

What’s next?

Studies to define biological versus demographic and socio-economic contributors to disparities are critical. It is also critical to establish and vigorously implement new methods for enrolling higher numbers of African American men and other minority groups onto clinical trials, so these groups may be appropriately represented.

For more information on PCF’s research initiatives specifically aimed at reducing health disparities, and how African American patients can get involved, please visit www.pcf.org/aari.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.