Pelvic floor muscle training (PFMT) and the use of duloxetine may not be the best options for recovering urinary continence after robotic-assisted radical prostatectomy (RARP), according to the randomized IMPROVE trial. “Of men who received no treatment at all, 53% recovered urinary continence 6 months after surgery compared with 35% of men in the PFMT arm (P=0.07) and 39% of men in the duloxetine arm (P=0.2, both statistical differences are not significant). A fourth arm combining PFMT and duloxetine had even poorer results, with just 27% of those men achieving urinary continence at 6 months (P=0.009),” reported Rafael Sanchez-Salas, MD, of McGill University in Montreal, during a late-breaking abstract session at the American Urological Association (AUA) virtual annual meeting. “Among men who recovered urinary continence, there was no difference in the time to recovery between the 4 arms,” he added. “Of note, neurovascular bundle (NVB) preservation was the only factor associated with continence recovery in the study (OR 3.5, interquartile range 1.2-10.3, P=0.02),” he said.

“Most people talk about how nerve-sparing robotic RP can help preserve sexual function,” Ash Tewari, MD, of the Icahn School of Medicine at Mount Sinai in New York, said Adrien Bernstein, MD, a urologic oncology fellow at Fox Chase Cancer Center in Philadelphia.

He and his colleagues conducted a retrospective, multi-institution cohort study comparing prostatectomy (RP) rates during the first COVID wave (March to May 2020) with rates during the same months in 2019. They used the Pennsylvania Urologic Regional Collaborative (PURC) – which gathers data from academic and private institutions in urban and rural settings – to evaluate men diagnosed with nmPCa.

Of the 647 men with localized PCa, 269 received care during the 2020 study period and 378 received care during the 2019 period, Bernstein reported at the American Urological Association (AUA) 2021 virtual Annual Meeting. In 2020, surgery was significantly less likely for Black than for White men (1.3 vs. 25.9%; P <0.001), despite similar COVID-19 risk factors, prostate biopsy pathology grade, and comparable 2019 surgery rates (17.7 vs. 19.1%; P=0.75).

On regression analysis, after adjustment for covariates, the odds of RP for Black men dropped to 6% in 2020 (odds ratio [OR], 0.06; 95% confidence interval [CI], 0.007-0.43; P = 0.006, a statistically significant difference), with no change for White men Plummeted in 2020

During the initial COVID-19 lockdown, the odds of Black men undergoing surgery for untreated nonmetastatic (nm) prostate cancer (PCa) dropped by 94%, but for White men, there was no change, new data shows. Before the pandemic, “there was no difference between White and Black patients in terms of getting the surgery,” said Adrien Bernstein, MD, a urologic oncology fellow at Fox Chase Cancer Center in Philadelphia.

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Androgen deprivation therapy (ADT) options for prostate cancer (PCa) seemed to have a similar impact on the risk of cardiovascular (CV) events among people with documented heart disease, according to results from the PRONOUNCE trial, although the study was terminated early due to slow accrual. “In 545 men, there was no statistically significant difference in the rate of a major adverse CV event (MACE) at 12 months between men treated with degarelix and those treated with leuprolide,” reported Renato Lopes, MD, of Duke University Medical Center in Durham, NC, at the European Society of Cardiology (ESC) virtual meeting. The degarelix group saw a 5.5% MACE rate vs. 4.1% in the leuprolide groups (P=0.53, not a statistically significant difference). This primary endpoint was defined as a composite of death, myocardial infarction, or stroke through 12 months. PRONOUNCE was set to recruit 900 men but, because of sluggish enrollment, settled at 545 (average age 73). “Previous research had indicated that gonadotropin-releasing hormone (GnRH) antagonists such as degarelix may be associated with a preferable CV safety profile,” Lopes explained.

PRONOUNCE was the first randomized clinical trial to prospectively compare the cardiovascular safety of a GnRH antagonist with a GnRH agonist (leuprolide) in men with PCa.

(Continued on page 6)
Real World Practice Patterns and Predictors of Continuous Versus Intermittent Androgen Deprivation Therapy Use for Prostate Cancer in Older Men

J Urol 206: 933-941, 2021

Purpose: Phase-III randomized control trial evidence suggests intermittent androgen deprivation therapy (IADT) is not significantly inferior to continuous androgen deprivation therapy (ADT) for men with prostate cancer (PCa). However, clinical practice and guidelines differ in their recommendations. We evaluate real-world use and practice patterns of IADT.

Materials and Methods: Ontario men ≥65 years of age with PCa who initiated ADT for ≥3 months were identified (1997-2017). Lapses in ADT ≥6 months (initial gap) and ≥3 months (subsequent gaps) were used to classify IADT. Neoadjuvant/adjuvant therapy was excluded. Disease stage adjustment was completed for men with likely metastatic disease based on de novo presentation with ADT. Patient and physician predictors of IADT were analyzed using multivariable logistic regression.

Results: We identified 8,544 men with 1,715 having previously received local therapy. Among all patients, 16.4% received IADT. This ranged from 11.4%-24.8% across health-planning regions and increased to 26.6% in those with previous local therapy. Mean follow-up was 8.3 years. Men with prior local therapy (odds Ratio [OR] 1.85, 95% Confidence Interval [CI] 1.59-2.17, p <0.001) and those in the highest income quintile (OR 1.32, 95% CI 1.08-1.60, p=0.005) had increased odds of receiving IADT. Radiation oncologists were more likely to use IADT than urologists (OR 1.99, 95% CI 1.59-2.50, p <0.001), as were physicians with more experience (≥210 years in practice: OR 1.44, 95% CI 1.11-1.88, p=0.007). In specialty-stratified analyses, case volume was significantly associated with IADT for radiation oncologists (highest quartile: OR 1.73, 95% CI 1.14-2.62, p=0.009).

Conclusions: IADT remains underutilized for men with PCa who are ≥65 years of age, with only 1 in 4 to 1 in 6 eligible patients receiving this form of care. Clinical, sociodemographic and physician characteristics play an important role in treatment selection.

Short Androgen Suppression and Radiation Dose Escalation in Prostate Cancer: 12-Year Results of EORTC Trial 22991 in Patients with Localized Intermediate-Risk Disease
Bolla M, Neven A, Maingon P, Boladeras CC, et al.

J Clin Oncol 39: 3022-3033, 2021

Purpose: The European Organisation for Research and Treatment of Cancer (EORTC) trial 22991 (NCT00021450) showed 6 months of concomitant and adjuvant androgen suppression (AS) improves event- (EFS, Phoenix) and clinical disease-free survival (DFS) of intermediate- and high-risk localized prostate carcinoma (PCa), treated by external-beam radiotherapy (EBRT) at 70-78 Gy. We report long-term results in intermediate-risk men treated with 74 or 78 Gy EBRT, as per current guidelines.

Patient and Methods: Of 819 men randomly assigned between EBRT or EBRT plus AS started on day 1 of EBRT, 481 entered with intermediate-risk (International Union Against Cancer TNM 1997 cT1b-c or T2a with PSA ≥10 ng/mL or Gleason ≤7 and PSA ≤20 ng/mL, NOM0) and had EBRT planned at 74 (342 men, 71.1%) or 78 Gy (139 men, 28.9%). We report the trial primary end point EFS, DFS, distant metastasis-free survival (DMFS), and overall survival (OS) by intention-to-treat stratified by EBRT dose at 2-sided α = 5%.

Results: At a median follow-up of 12.2 years, 92 of 245 men and 132 of 236 had EFS events in the EBRT plus AS and EBRT arm, respectively, mostly PSA relapse (48.7%) or death (45.1%). EBRT plus AS improved EFS and DFS (hazard ratio [HR] = 0.53; CI, 0.41 to 0.70; P <0.001 and HR = 0.67; CI, 0.49 to 0.90; P = 0.008). At 10 years, DMFS was 79.3% (CI, 73.4 to 84.0%) with EBRT plus AS and 72.7% (CI, 66.2 to 78.2%) with EBRT (HR = 0.74; CI, 0.53 to 1.02; P = 0.065). With 140 deaths (EBRT plus AS: 64; EBRT: 76), 10-year OS was 80.0% (CI, 74.1 to 84.7) with EBRT plus AS and 74.3% (CI, 67.8 to 79.7) with EBRT, but not statistically significantly different (HR = 0.74; CI, 0.53 to 1.04; P = 0.082).

Conclusion: Six months of concomitant and adjuvant AS statistically significantly improves EFS and DFS in intermediate-risk PCa, treated by irradiation at 74 or 78 Gy. The effects on OS and DMFS did not reach statistical significance.
I need to let you know that I received some groovy and far out (aka 1960s and 1970s vernacular meaning “I liked them”) letters about my COVID-19 column over the past year. However, I took a tiny break from writing that specific column because I want my spouse to stay married to me and because there are multiple other projects that also needed some immediate attention, but COVID-19 education is still a major priority for me. So, let’s dedicate the column this month to one of the most unsung and underutilized COVID-19 websites in the past year, and it is a wonderful contribution from the U.S. Department of Health and Human Services (HHS). They did something amazing in early 2021, but it needs far more attention! PLEASE TELL YOUR FRIENDS (capital letters do not mean shouting in the Moyad vernacular, but rather “pretty please with no sugar on top tell your friends”) and talk to your health care team about it! HHS launched the COVID-19 antibody treatment locator website (SEE FIRST REFERENCE BELOW and/or type in “HHS Treatment Locator” in Google, etc.), which can help you, cancer patients, and health care professionals find specific outpatient monoclonal antibody treatment centers near you, whether you are at home or traveling, especially in the United States. If you are not living in the U.S., then ask your local health system or public health agency where you can get them. Again, one of the challenges this year has been the lack of knowing where people at higher risk of getting severe COVID-19 can go to get antibody treatment if they are diagnosed with this condition. Emergency room? Urgent care? Medical office? Infusion center? Yes, in some geographic regions, and not in others, depending on where you live, work, or are vacationing. For example, I need to go to Florida soon to visit my mom and I already can tell you where she can get them just 15 miles from where she lives by simply typing the name of her city in the site on the HHS treatment locator website. The treatments have been a miracle for so many high-risk of COVID progression people especially when used within the first few days of symptoms (earlier is better). These incredible proteins were created by several companies in the laboratory and can bind to the virus, reduce its severity and transmission, and simply prevent something mild-to-moderate from becoming severe. The onetime infusion takes 30-60 minutes to administer, followed by an observation period, then that is it. Wow and wow spelled backwards! People love to use the jaded term “game changer” for almost anything today, for example, “hey that meal was a game changer,” but adding more and more antibody treatment locations near you (aka HHS TREATMENT LOCATOR) is a potential game changer. Cancer patients are at higher risk of COVID-19 severity and complications compared to many other folks not dealing with cancer, so knowing precisely where you can get an antibody treatment near you, if needed, or if you are traveling is a real “game changer” for cancer patients! And please also talk to your healthcare team about whether you specifically qualify, and some of the best local places to receive it apart from what the website says. In fact, a recent wonderful small study of cancer patients at UCSD (University of California San Diego) is giving us some idea of how incredibly helpful these things could be for some high-risk cancer patients diagnosed with COVID-19, should they receive antibody treatment within days of a COVID-19 diagnosis.2
At the time of this writing, there are a few monoclonal antibody products with Emergency Use Authorizations (EUAs) from the FDA for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed COVID-19 infection. Interestingly, one of them known as “sotrovimab” (from GSK company) was originally first isolated and derived from a SARS-1 survivor in 2003! Another monoclonal antibody known as “casirivimab plus imdevimab” – also known as “REGEN-COV” (aka the Regeneron product) was even recently given the green light to be given in some high-risk individuals exposed to someone with COVID-19. Additionally, as I was just submitting this column, another monoclonal treatment known as bamlanivimab plus etesevimab (Eli Lilly) became available again.
Now there is breaking news on the drug remdesivir (also known as Veklury) marketed by Gilead Sciences, Inc. Just as this issue of the Hot SHEET was going to press, Gilead announced positive results from a Phase 3 randomized, double-blind, placebo-controlled trial that studied the efficacy and safety of a 3-day course of intravenous remdesivir for the treatment of COVID-19 in nonhospitalized patients at high risk for disease progression. In an analysis of 562 participants randomly assigned in a 1:1 ratio to remdesivir or placebo, the drug demonstrated a statistically significant 87% reduction in risk for the composite primary endpoint of COVID-19-related hospitalization or all-cause death by Day 28 (0.7%, [2/279]) vs. placebo (5.3%, [15/283]) p=0.008.
Of course, none of this stuff is a substitute for vaccination, but it adds to your list of important empowerment items. So, now it is your turn, because you are reading this column somewhere on the planet right now, so do you know where you could go right now if you needed monoclonal antibody treatment? Can you name at least 2-3 treatment facilities close to where you live right now? If not, then you know why I wrote this column, and if you did know then good for you, and please pass on that information. Thank you and now we will return to our regularly scheduled column.

References:
Paul Viscuse, MD, a second-year hematology-oncology fellow at the University of Texas MD Anderson Cancer Center in Houston, was chosen by the Journal of Clinical Oncology for its 2021 Conquer Cancer Young Investigator Award.

As the journal explained, the honor, first awarded in 1984, provides funding to promising investigators to promote quality research in clinical oncology. The purpose is to fund physicians transitioning from a fellowship program to a faculty appointment as a way to encourage young investigators to pursue careers in clinical oncology research. Viscuse’s research focuses on androgen-indifferent prostate cancer (AIPC). These cancers are resistant to therapies that target androgen receptor signaling, and there is a lack of alternative therapies effective against AIPC. In the following interview, Viscuse talked about his interest in AIPC and his research into more effective therapies.

ASCO: What drew you to study AIPC in particular?

Viscuse: I became interested in AIPC early in my fellowship at MD Anderson under the mentorship of Dr. Ana Aparicio. Many men with metastatic PCa experience an indolent disease course with long-term survival following prolonged responses to systemic therapies, most of which are directed towards disrupting androgen receptor (AR) signaling.

However, PCa has been increasingly recognized as a heterogeneous disease with a subset of men having rapid disease progression despite therapy, resulting in poor clinical outcomes. Androgen indifference has been classically associated with variant histology, such as small cell or neuroendocrine PCa (SCPC/NEPC). Yet an increase in biopsies of metastases has revealed an increased prevalence of adenocarcinoma histology despite atypical clinical features.

Dr. Aparicio has conducted a series of clinical trials and parallel studies in patient-derived xenograft models to define clinical and molecular features of the aggressive variant PCa (AVPC) to capture tumors that poorly respond to AR-directed therapies and enrich for a population that benefits from platinum-based chemotherapy. This has provided a framework that can potentially enable the development of biomarkers and novel therapies for this subset of patients. During my fellowship, I have had the opportunity to report outcomes and conduct correlative studies from recently completed clinical trials led by Dr. Aparicio that have reinforced my interest in AIPC and his research into more effective therapies.

ASCO: What are some of the chief variants of AIPC, and how common are they?

Viscuse: There are morphologic variants of PCa, such as SCPC/NEPC, which may arise pure or admixed with adenocarcinoma, demonstrate virulent clinical courses, and do not typically respond to AR-directed therapy but respond to platinum-based chemotherapy.

When occurring de novo, these tumors are quite rare, with small series estimating a prevalence of 1-2%, though treatment-emergent NEPC may arise on metastatic biopsies after the patient has been treated with AR-directed therapy for adenocarcinoma in an approximately 10-20% of cases. Atypical clinical features seen with the morphologic variants can also be seen in conventional prostate adenocarcinoma, with or without the expression of neuroendocrine markers. One example is a recently described subset (approximately 20%) of castrate-resistant PCa tumors demonstrating androgen indirection following an initial response to AR-signaling inhibition that lack expression of both AR and neuroendocrine markers, termed double-negative PCa.

Due to significant overlap among these tumors, the AVPC as described by Dr. Aparicio attempts to compile clinicopathologic criteria characteristic of the SCPC/NEPC to allow for patient selection, regardless of morphology.

(Continued on page 7)

Best Way to Recover Urinary Continence Post-RP (Continued from page 1)

stated. “An important study finding is that NVP is also important for improving urinary continence outcomes.” From 2015 to 2018, the IMPROVE study evaluated 240 men with organ-confined prostate cancer (PCa) with post-RP urinary incontinence. They were randomized to 4 arms of 60 men each: 1 with no treatment (control arm), 1 with duloxetine alone (60 mg at bedtime for 3 months), 1 with PFMT alone (pelvic muscle contractions with biofeedback weekly for 3 months), and 1 combining PFMT with duloxetine. The primary study endpoint was continence at 6 months, defined as no urine leakage for 3 consecutive days. Secondary endpoints included urinary symptoms and quality of life (QoL), as assessed by a visual analog scale (VAS), the International Prostate Symptom Score (IPSS), and the King’s Health Questionnaire.

Of the men in the study, 89% completed a year of follow-up. In the duloxetine arms, 58% of men had properly taken the drug, while 38% of men in the PFMT arms trained at least 10 weeks. IPSS revealed a large proportion of men suffering moderate to severe urinary symptoms, 30% in the duloxetine alone arm, 27% in the PFMT arm, and 24% in the combination arm compared with 11% in the control arm. As for QoL by the VAS, 17% of men in the control group reported being uncomfortable or worse vs. 45, 44, and 38% of men in the duloxetine, PFMT, and combined arms, respectively.

“Based on our results we do not routinely recommend these interventions for men after RARP,” Sanchez-Salas concluded. “NVB preservation was the only factor found to be associated with continence recovery, pointing to the importance of a clean and precise surgical intervention to improve functional outcomes.”

Reference:
Presented at the 2021 AUA virtual annual meeting; abstract LBAO2-08
MedPage Today
13 September 2021
Old Saying About Prostate Cancer Not True When it’s Metastatic

Nearly 80% of men with metastatic prostate cancer (mPCa) died from their malignancy, according to a retrospective cohort study involving 26,000-plus American men diagnosed with advanced disease in roughly the last 20 years.

“The findings fill an information gap because, remarkably, data are lacking on causes of death among men whose PCa has spread to other sites,” say lead author Ahmed Elmehrath, MD, of Cairo University, Cairo, Egypt, and colleagues.

“Most men with mPCa die from it, rather than other possible causes of death,” confirm editorialists Samuel Merriel, MSc, Tanimola Martins, PhD, and Sarah Bailey, PhD, University of Exeter Medical School, Exeter, UK.

The study was published online August 5th in JAMA Network Open.

The study’s findings show the near opposite of a commonly held belief about early-stage disease: “You die with PCa, not from it.”

However, these commonplace comments do not cover metastatic disease, which is what the authors of the new study decided to focus on.

The team used Surveillance, Epidemiology, and End Results Program (SEER) data to gather a sample of 26,168 US men diagnosed with mPCa from January 2000 to December 2016. They then analyzed the data in 2020 and found that 16,732 men (64%) had died during follow-up.

Most of these deaths (77.8%) were from PCa, 5.5% were from other cancers, and 16.7% were from noncancer causes, including cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and cerebrovascular diseases. Most of the PCa deaths (59%) occurred within 2 years. The 5-year overall survival rate in the study group was 26%.

Senior author Omar Alhalabi, MD, of University of Texas MD Anderson Cancer Center, acknowledged a limitation in these findings – that the SEER database relies on causes of death extracted from death certificates. “Death certificates have limited granularity in terms of the details they can contain about the cause of death and also have reporting bias,” he said.

The mean age at mPCa diagnosis in the study was roughly 71 years. Most of the cohort was White (74.5%) and had a diagnosis of stage M1b mPCa (72.7%), which means the cancer had spread to the bones. Among men in the cohort, the death rates from septicemia, suicide, accidents, COPD, and CVD were significantly increased vs. the general US male population.

Thus, the study authors were concerned, not only with death from mPCa, but death from other causes. That concern is rooted in the established fact that there is now improved survival among men with PCa in the US, including among men with advanced disease. “Patients tend to live long enough after a PCa diagnosis for noncancer-related comorbidities to be associated with their overall survival,” they write.

The editorialists agree: PCa “has a high long-term survival rate compared with almost all other cancer types and signals the need for greater holistic care for patients.” As noted above, CVD was the most common cause of non-PCa-related deaths in the new study.

As in the management of other cancers, there is concern among clinicians and researchers about the cardiotoxic effects of androgen deprivation therapy. Authors point to a 2017 analysis that showed that men with PCa and no prior cardiac disease had greater risk of heart failure after taking ADT.

The authors of the current study say that such findings highlight “the importance of multidisciplinary care for such men and the role of primary care physicians in optimizing cardiovascular risk prevention and providing early referrals to cardiologists.” Further, the team says that tailoring “ADT to each patient’s needs may be associated with improved survival, especially for men with factors associated with CVD.”

Who should lead the way in multidisciplinary care? “Case-by-case may be the answer,” said Alhalabi, adding it may depend on underlying morbidities, e.g., CVD and COPD. The deadliness of metastatic disease “reinforces the need for innovations to promote early-stage diagnosis,” comment the editorialists. Strengthening the hope, they say, is “new tests for PCa detection may reduce the proportion of men who receive a diagnosis at a late stage.”

Medscape Medical News
02 September 2021

Plant-Based Diet Tied to Better Urological Health

“Eat More Plants for Your Prostate and Erections”

Men interested in preserving their urological health may benefit from eating more vegetables and fruits, researchers reported.

A trio of studies presented at the American Urological Association (AUA) virtual meeting suggested that plant-based diets were associated with a decreased risk of erectile dysfunction (ED), lower PSA rates, and possibly a lower rate of total and fatal prostate cancer (PCa) among younger men.

“We can summarize this session succinctly,” said AUA press conference moderator Stacy Loeb, MD, of NYU Langone Health in New York City, who also presented one of the studies. “Eat more plants for your prostate and your erections,” she advised.

Investigators at the University of Miami (UMiami) Miller School of Medicine used the National Health and Nutrition Examination Survey (NHANES) to evaluate the association between a plant-based diet and PSA. Using Food Frequency Questionnaire dietary data they calculated a plant-based diet index (PDI) and healthful plant-based diet index (hPDI).

Ali Mouzannar, MD, reported that in a cohort of 1,399 men, those with a higher consumption of healthy plant-based diet (high hPDI scores) had a decreased probability of having an elevated PSA (OR 0.47, 95% CI 0.24-0.95).

“It seems plant-based diets have protective effects against PCa,” Mouzannar said during the press session. “We still need more insight and more clinical trials to establish the causative effect, but there have been multiple associations between lower risk of PCa, lower risk of elevated PSA with a plant-based diet.”

(Continued on page 8)
Darolutamide was linked with a decrease in locally invasive procedures, as well as local urinary and bowel symptoms, in men with non-metastatic (nm) castration-resistant prostate cancer (CRPC), according to an analysis of the ARAMIS trial.

“The drug, compared with placebo, was also associated with a delayed deterioration in patient quality of life (QoL) related to urinary and bowel symptoms,” reported Neal Shore, MD, Carolina Urologic Research Center, SC at the American Urological Association 2021 virtual Annual meeting. “These findings demonstrate that [darolutamide] had a positive effect on local disease recurrence and symptom control in nmCRPC,” Shore said.

Darolutamide is an androgen receptor inhibitor (ARI) that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. Based on results from ARAMIS, FDA approved the agent for the treatment of nmCRPC in 2019, with overall survival (OS), and secondary outcome, data added to the approval label in January 2021. In the trial, 1,509 men with nmCRPC were randomized 2:1 to receive either darolutamide or placebo. Darolutamide was shown to significantly increase metastasis-free survival (MFS) in these patients, as well as OS, compared with placebo.

“Urinary and bowel problems frequently occur with progression of localized PCa and can interfere with patients’ QoL,” Shore said. “Thus, it is important for treatment of nmCRPC patients to not only delay metastasis and prolong survival, but also control associated symptoms and prevent QoL.”

Shore and his colleagues evaluated the effectiveness of darolutamide on 3 aspects of local symptom control in ARAMIS patients:

- Incidence and time to first PCa-related locally invasive procedures.
- Time to QoL deterioration in urinary and bowel symptoms, as measured by the EORTC QoL questionnaire PCa module, and FACT-P PCa subscale (PCS).
- Incidence of urinary and bowel adverse events (AEs) between treatment groups, and correlation of AEs with PSA decline from baseline to 16 weeks in the darolutamide arm.

Shore and colleagues found that fewer men receiving darolutamide (4.7%) underwent locally invasive procedures than men receiving placebo (9.6%), and that darolutamide was also associated with significantly prolonged time to first procedure vs. placebo (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.28-0.62).

As measured with the EORTC-QLQ-PR25 subscales and compared with placebo, darolutamide significantly delayed the time to QoL deterioration of total urinary symptoms (25.8 vs. 14.8 months, HR 0.64, 95% CI 0.54-0.76) and for each of the separate urinary symptom questions, as well as delayed the time to deterioration for total bowel symptoms (18.4 vs. 11.5 months, HR 0.78, 95% CI 0.66-0.92), along with each of the bowel symptom questions.

On the FACT-P PCS, darolutamide delayed time to deterioration of all urinary symptoms (11.1 vs. 7.9 months, HR 0.80, 95% CI 0.70-0.91) and for each of the separate urinary symptom questions. However, time to deterioration in trouble moving bowel was not significantly impacted by treatment.

There was little difference between the darolutamide and placebo groups in the incidence of AEs for urinary tract infection (5.3 vs. 5.6%), abnormally frequent urination (4.4 vs. 3.2%), and hematuria (4.5 vs. 5.4%). However, the incidence of AEs was lower for darolutamide vs. placebo for urinary retention (3.8 vs. 7.4%) and dysuria (2.6 vs. 5.2%).

Among darolutamide patients, the greater the PSA response, the lower the incidence of urinary retention and dysuria. For men with >90% PSA response, the incidence of urinary retention and dysuria was 2.2 and 0.5%, respectively, vs. 5.1% for both of these AEs in men with <50% PSA response.

“No increase in urinary- and bowel-related adverse events compared with placebo confirms the favorable safety profile of darolutamide,” Shore observed.

“Patient reported QoL is one of the most important aspects of clinical decision making, both for physicians and patients,” noted Alicia K. Morgans, MD, MPH, of Dana-Farber Cancer Institute in Boston, who was not involved in the study. “It is great to see this deeper dive into QoL outcomes in ARAMIS as they provide a clearer view of what men can expect if treated with darolutamide for nmCRPC,” she said.

“Not only can these relatively asymptomatic men expect to largely maintain QoL, but some may even have improved urinary and bowel complaints, which are some of the most common issues facing this population,” Morgan pointed out. “Early treatment of nmCRPC remains of high importance, not just to prolong MFS and OS, but to maintain, and possibly improve, life for these men.”

Presented at the 2021 virtual AUA annual meeting:
abstract# PD34-10
MedPage Today
12 September 2021

Prostatectomies Plummeted for Black Men in 2020
(Continued from page 1)

men (OR, 1.41, 95% CI, 0.89-2.21; P=0.142). “In a multivariable analysis, adjusted for the presence of high-risk disease and age, White men were 31 times more likely to receive surgical care during the lockdown period than Black men,” Bernstein said.

“Early in the pandemic, many resources were diverted from cancer care to COVID care, leaving many patients, including those with PCa, with limited or no access to surgery,” he explained. “Although localized PCa does not require immediate treatment, the study highlights systemic inequities,” the team writes in their abstract.

“The degree to which sites reduced surgery during the first wave varied substantially, with some sites increasing surgical volume by 33% and others shutting down completely,” said Bernstein.

“Notably, the lockdown had the greatest impact on sites that cared for more Black men. Lessons from the study apply to all patients and should drive efforts to recognize and offset the implications of our pandemic-

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Clinical criteria includes any of the following: (1) presence of exclusive visceral (bowel) metastases; (2) predominantly lytic bone metastases; (3) bulky (≥5 cm) tumor masses, including lymphadenopathy (lymph node enlargement) or high-grade tumor masses in the prostate or pelvis; (4) low PSA relative to tumor burden, specified as a PSA of 10 ng/mL or less at initial presentation (before ADT) or at the time of symptomatic progression of castrate-resistant disease plus high-volume (20 or more) bone metastases; (5) serum carcinoembryonic antigen (CEA) and/or lactate dehydrogenase (LDH) twice the upper limit of normal; (6) short interval (≤6 months) to castration-resistant progression following initiation of hormonal therapy; and (7) SCPC/NEPC morphology.

Approximately 30% of men with lethal metastatic CRPC meet these criteria, and the number of criteria met has been significantly associated with shorter survival independent of neuroendocrine marker expression. Molecular studies of tumors meeting these criteria indicate that they may be characterized by two or more alterations in the tumor suppressors TP53, RB1, and PTEN.

ASCO: One therapy you are investigating is PEGylated arginine deiminase (ADI-PEG20). How does this drug work?

Viscuse: L-arginine serves as a precursor for several critically important substances including nitric oxide, creatine, polyamines, and other amino acids. The urea cycle normally generates endogenous arginine, making it a semi-essential amino acid.

Many tumors demonstrate urea cycle dysregulation by downregulating the rate limiting urea cycle enzyme argininosuccinate synthetase (ASS1) which leads to an auxotrophic reliance on extracellular arginine. ADI-PEG20, developed by Polaris Group, is a PEGylated arginine deiminase derived from the bacterium Mycoplasma hominis that depletes circulating arginine, leading to autophagy and apoptosis in auxotrophic tumor cells.

Early clinical trials indicate that ADI-PEG20 is safe and tolerated in humans while demonstrating activity in the treatment of various malignancies.

ASCO: Tell us about the research you are doing with this drug.

Viscuse: Although initially tumors respond to ADI-PEG20, they eventually reexpress ASS1, leading to resistance. As a result, interest has shifted to combining ADI-PEG20 with other anticancer agents. Preclinical studies demonstrated a concentration-dependent downregulation of ASS1 with cisplatin treatment in lung cancer, ovarian cancer, and melanoma cell lines.

As mentioned earlier, the AVP attempts to enrich for platinum-sensitive prostate cancer, making it ideal for the study of ADI-PEG20 and platinum chemotherapy. Using available tumor specimens collected from completed clinical trials, I plan to measure urea cycle metabolites and enzyme expression to see if there is an association between urea cycle dysregulation and tumors meeting AVPC criteria. In the laboratory of Dr. Dan Frigo, I am testing for a similar dose-dependent downregulation of ASS1 expression with platinum chemotherapy in several PCa cell lines.

Prostatectomies Plunged for Black Men in 2020

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Mouzannar explained during a press briefing, “so access to the most cutting-edge treatments is critical.”

“This drop in surgeries is jarring,” said Brian K. McNeil, MD, MBA, associate dean for clinical affairs and vice chair of the Department of Urology at SUNY Downstate Health Sciences University in Brooklyn, New York. “Because the pandemic struck urban areas particularly hard, Black men might have had less access to surgery because of where they live. Still, it was a bit shocking,” he stated.

“Access to sipuleucel-T was no doubt complicated by the high price and the cultural mistrust surrounding a drug in which cells are essentially harvested, reprogrammed to attack cancer cells, and put back in the body,” he said.

“But the bottom line is that all races must have equitable access to the most promising treatments. Both these studies, along with others presented at the AUA meeting, drive home the point that disparities do exist,” McNeil said. “Research on the underlying roots of disparities and education is needed. We need to educate not only patients, but also urologists ourselves, about disparities,” he said.

Presented at the AUA 2021 virtual Annual Meeting; abstracts PD03-02, PD34-03

Medscape Medical News 11 September 2021

I also plan to select a few candidate AVPC patient-derived xenograft models designed at our institution and treat them with platinum-based chemotherapy and ADI-PEG20 to assess for higher efficacy with the combination, while also measuring pre- and post-treatment urea cycle metabolites and enzyme expression.

The findings of these studies could inform a future early phase clinical trial using ADI-PEG20 and platinum-based chemotherapy in men meeting AVPC criteria and may also uncover other altered metabolic pathways amenable to therapeutic exploitation.

References:
MedPage Today 08 September 2021
ADT Options for Prostate Cancer Come Out Even for Heart Safety (Continued from page 1)

At some point in their illness, about 50% of men with PCa will be prescribed ADT, such as orchieotomy, testosterone antagonists, or modulation of the GnRH. ADT is associated with heart disease and stroke, particularly with pre-existing CV disease (CVD). More than 1 million men globally are diagnosed with PCa every year, and these men are at high risk of developing CVD, as well as more likely to die from the latter than their healthy peers.

“There is an ongoing need to understand the CV effects of oncological treatments as cancer survivorship increases and competing non-cancer death becomes more likely,” Lopes said in a press release. “PRONOUNCE provides a model for the interdisciplinary collaboration between oncologists and cardiologists with a shared goal of evaluating the impact of cancer therapies on CV outcomes.”

ESC spokesperson Sarah Clarke, MD, of Royal Papworth Hospital in Cambridge, UK, agreed, declaring, “This is a really good example of how medical teams have to work together – cardiologists, oncologists, urologists,” she said. “We have to work more as a team than we used to do. The selection of treatments requires engagement from the wider community.”

As for choosing between a GnRH antagonist and a GnRH agonist in the context of CV health, “There are 2 perspectives on this,” commented ESC press conference moderator Carlos Aguiar, MD, of Hospital Santa Cruz in Lisbon, Portugal. “One is from the cancer side and the other is the CVD side. The oncology part of the side should be left to the oncologists. This was more a CV story. “ADT is employed because it deprives the cancer cell of the hormones needed for growth,” he added. “But in doing this, you want to be sure that there is no higher risk for CVD, so you want to make sure these drugs are CV safe. In this case, the 2 treatments were similar so I think both are equally safe as major CV event points go.”

MedPage Today 31 August 2021

Plant-Based Diet Tied to Better Urological Health in Men (Continued from page 5)

He added that “it also works the other way around – meat has been shown to be associated with a high rate of aggressive PCa, and high risk of recurrence.”

Loeb and colleagues conducted a prospective study involving 27,243 men followed up to 28 years, in the Health Follow-up study. They found that in men ages ≤65 at diagnosis, greater overall consumption of plant-based diet was associated with a lower risk of advanced PCa (HR 0.68, 95% CI 0.42–1.10). Among younger men, it was associated with lower risks of PCa (HR 0.81 95% CI 0.70-0.95), and fatal disease (HR 0.53, 95% CI 0.32-0.90).

“This is really encouraging given the many health and environmental benefits of plant-based diets,” Loeb said. “And we believe they should be recommended for men who are concerned about the risks of prostate cancer.”

Mouzannar noted “There is a significant effect in following plant-based diets,” he said. “Whether that’s in individuals by promoting a healthy lifestyle and decreasing the risk of multiple cancers in addition to PCa.”

“I see it as a win-win,” Loeb said. “There’s not really a downside here. You’re going to decrease your risk of aggressive PCa and elevated PSA, and increase your chances of preserving erectile function, and it’s just better for the planet.”

Presented at the AUA 2021 virtual Annual Meeting; abstract PD20-05 MedPage Today 12 September 2021
QUESTION FROM PROSTATE CANCER SURVIVOR:
Can L-arginine help with my erectile dysfunction?

RESPONSE FROM DR. ANNE KATZ:
L-arginine is an amino acid that helps with the production of proteins in the body. The body itself produces sufficient amounts of this amino acid to take care of the body’s needs. There is NO evidence that, taken as a supplement, L-arginine is helpful for erectile functioning. It is broken down in the body to nitric oxide (NO) that helps blood vessels to relax, and this is why the inaccurate belief exists that it can help with erections.

This supplement has side effects that deserve attention. There is a risk of increased bleeding and changes in blood sugar levels. If you take blood thinners you should not take L-arginine as it increases your risk of bleeding, and if you have had a previous heart attack, taking L-arginine may increase your risk of death.

It can also decrease your blood pressure to unsafe levels. L-arginine should not be taken if you are using any of the oral medications to treat ED, such as Viagra, Cialis, etc. It can also cause nausea, bloating, abdominal pain, and diarrhea. Men who have asthma should not take this supplement as it can worsen breathing. It can also trigger herpes if you have previously had an outbreak.

People often assume that vitamins and minerals are ‘natural’ and ‘safe’ but, as you can see, there are significant risks, just as there are risks with conventional/medical treatments.

Watch Dr. Katz’s presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018 at: https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.

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:  ustooBTS@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
Des Plaines, IL 0018
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. This regular Hot SHEET supplement 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.

The Complex, Natural Biochemistry of a Healthy Diet
During Prostate Cancer Awareness Month, the Prostate Cancer Foundation hosted a webinar, “The Science of Nutrition and Prostate Cancer.” The accomplished nutrition researcher Prof. Richard Mithen presented an overview of diets and foods that have been linked to a lower risk of cancer and, in some cases, prostate cancer. Mithen, professor of nutrition at the University of Auckland and PCF Challenge Award recipient, has been a leader in this field for decades.

Prof. Mithen began with the “Big Picture” by outlining the benefits of plant-based and Mediterranean diets, emphasizing the importance of eating a large variety of plant-based foods. Oily fish, such as salmon, is a healthier animal protein alternative. These general principles, along with regular exercise, offer a path to good overall health.

He further discussed a variety of fruits, vegetables, protein sources, and even spices that have the potential to affect health, and possibly prostate cancer specifically. Although it’s tempting to believe that diet is an exact science, there is a lot of complex biochemistry associated with it. Unlike taking a medicine (a high concentration of one molecule made to target a specific protein or chemical reaction in the body), diet means that you eat small amounts of a large number of molecules, creating an intricate web of reactions with many changing variables. Broccoli, for instance, contains many phytochemicals and nutrients in addition to cancer-fighting glucoraphanin, including fiber, vitamins, and minerals. All of these affect the body in some capacity, and may differ somewhat from person to person.

Broccoli remains at the forefront of Prof. Mithen’s research, as current evidence suggests that it offers meaningful potential to reduce prostate cancer risk or risk of cancer progression. This is because broccoli contains glucoraphanin, which is converted to the active molecule sulforaphane by the bacteria in your gut. Within a few hours, sulforaphane is absorbed throughout the body and accumulates in the prostate gland. Sulforaphane has general health benefits due to its ability to turn on hundreds of genes in the liver associated with anti-oxidant defense, anti-inflammation, and the excretion of foreign pollutants. Beyond that, sulforaphane may impact the prostate by fighting the growth of tiny cancers that have the potential to become larger. Prof. Mithen has developed new varieties of broccoli with different amounts of glucoraphanin, including those with up to 7 times higher amounts than regular broccoli. In a PCF-funded study, men with localized prostate cancer on active surveillance consumed a “broccoli soup” weekly. After 12 months, men who ate the broccoli soup containing the highest amounts of glucoraphanin had reduced changes of expression in their prostate gland of genes that are thought to drive cancer progression, suggesting that glucoraphanin (sulforaphane) may indeed affect the risk of aggressive prostate cancer.

While there is no dietary magic bullet—not even broccoli—lifestyle changes including more plant-based foods, less red meat and dairy, and increased exercise lead to better health, and certainly will not cause harm. Examples of foods containing important phytonutrients include: broccoli, turmeric, tomatoes, garlic, Brussels sprouts, and berries... and there are so many more to choose from.

You can see Prof. Mithen’s talk along with the full webinar at https://www.pcf.org/webinar-series/.

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