PARP inhibitors: What urologists need to know

In May 2020, the FDA approved the oral poly (ADP-ribose) polymerase (PARP) inhibitors rucaparib (Rubraca) and olaparib (Lynparza) for the treatment of metastatic castration-resistant prostate cancer. These 2 novel treatments represent the first approvals in this class of medications for prostate cancer. In this interview, Emmanuel S. Antonarakis, MD, provides an overview of these treatments, discusses the key trials that led to their approvals, and explains the urologist’s role in their use.

Q: Could you provide an overview of PARP inhibitors? How do they work?
A: PARP inhibitors work on a principle called synthetic lethality. Briefly, PARP inhibitors increase the lethality. Briefly, PARP inhibitors increase the lethality.
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Chairman’s Letter

MICHELE HENNESSY SR
Mike Hennessy Sr is chairman and founder of Urology TimesSM parent company, MJH Life SciencesSM.

When I look back at the key milestones in urology from 2020, one story that immediately comes to mind is the FDA’s approvals of the first (ADP-ribose) polymerase (PARP) inhibitorsrucaparib (Rubraca) and olaparib (Lynparza) for the treatment of metastatic castration-resistant prostate cancer. They represent the first approvals in this class of medications for prostate cancer. For this month’s cover feature, we spoke with Emmanuel S. Antonarakis, MD, of Johns Hopkins Sidney Kimmel Comprehensive Cancer in Baltimore, Maryland. In the interview, Antonarakis provides an excellent overview of PARP inhibitors and how urologists will be involved with their use.

PARP inhibitors for prostate cancer take center stage

MIKE HENNESSY Sr

Data suggesting that the β₃-adrenoceptor agonist mirabegron, approved by the FDA for treatment of overactive bladder (OAB), may improve erectile dysfunction in men taking the treatment. Also in OAB, look for coverage of a recent study further examining the risk of dementia in patients taking anticholinergic medications for the condition.

Coding Q&A columnists Jonathan Rubenstein, MD, and Mark Painter tackle several different topics for this month’s installment, ranging from an update on chronic condition code G2211 to whether the COVID-19–related code 99072 is being reimbursed. For Money Matters, Jeff Witz, CFP, sets up 8 planning priorities so you can hit the ground running for your financial year. And in Speak Out, 3 urologists discuss dusting versus basketing for treating kidney/ureteral stones.

Urology TimesSM Clinical Practice Board member Henry M. Rosevear, MD, contributes a thoughtful piece on the thorny issue of real-time patient access to physician notes. Rosevear writes, “I have no problem with patients seeing everything in their chart. It is their medical record, after all. But I do think there should be some limitations on this access.”

We close this month’s issue with a fascinating Malpractice Consult column from Acacia Brush Perks, Esq. She discusses a case involving a man who received a diagnosis of metastatic prostate cancer and subsequently sued his urologist. The defendant-urologist claimed that the patient-plaintiff failed to timely return for a follow-up. “Many states recognize the defense of contributory negligence in medical malpractice cases. Disregarding a doctor’s orders can be patient negligence,” Perks writes.

In next month’s issue, watch for coverage of the 2021 Genitourinary Cancers Symposium. Thanks for reading! 01

REFERENCE
FDA approves label update for darolutamide in nonmetastatic CRPC
The FDA has approved a supplemental new drug application updating the label for darolutamide (Nubeqa), an oral gonadotropin-releasing hormone (GnRH) receptor antagonist for advanced prostate cancer (CRPC) to include overall survival (OS) data from the pivotal phase 3 ARMIS trial (NCT02200614).1
In the ARMIS trial, adding darolutamide to androgen deprivation therapy (ADT) reduced the risk of death by 31% compared with ADT plus placebo in men with nonmetastatic CRPC (HR, 0.69; 95% CI, 0.53-0.88; P = .003).2 At a median follow-up of 29 months, the 3-year OS rates were 93% and 77% in the darolutamide and placebo arms, respectively.
This OS benefit was reached even though over half (55%) of the patients on the control arm received darolutamide (n = 170) or other subsequent treatments (docetaxel, abiraterone acetate [Zytiga], enzalutamide [Xtandi], sipuleucel-T [Provenge], and cabazitaxel [Jevtana]) after the study was unblinded.
In addition to improving OS, the darolutamide regimen led to statistically significant delays in the time to first symptomatic skeletal event (HR, 0.48; P = .005), time to pain progression (HR, 0.65; P = .0001), and time to initiation of cytotoxic chemotherapy (HR, 0.58; P < .0001).

REFERENCES

New drug application is submitted for novel oral TRT for hypogonadism
Marius Pharmaceuticals has submitted a new drug application (NDA) to the FDA for SOV2012-F1 (Kyzatrex), an oral testosterone undecanoate soft gelatin capsule, for the treatment of adult men with primary or secondary hypogonadism.3
The NDA is based on a pivotal phase 3 trial, the results of which have not yet been made available. Marius Pharmaceuticals said it intends to share the data at medical meetings this year.
In a news release, Marius Pharmaceuticals noted that more than 96% of patients enrolled in MRS-TU-2019EXT who completed 90 days of treatment reached average testosterone levels in the normal range.

REFERENCES

FDA approves combination nivolumab/cabozantinib in RCC
The FDA has approved the combination regimen of nivolumab (Opdivo) plus cabozantinib (Cabometyx) as a frontline treatment for patients with advanced renal cell carcinoma (RCC).5
The approval is based on findings from the phase 3 CheckMate 9ER trial (NCT034177). Study results showed that the combination reduced the risk of disease progression or death by 49% versus sunitinib (Sutent) in treatment-naive patients with advanced RCC, with a median progression-free survival of 16.6 months versus 8.3 months, respectively (HR, 0.51; P < .0001).
Additional findings showed that, at a median follow-up of 18.1 months, the median overall survival was not reached in either arm, and there was a 40% reduction in the risk of death with the combination (HR, 0.60; P = .0001).
Cabozantinib was approved by the FDA in December 2017 for use in previously untreated patients with advanced RCC. The FDA approved nivolumab in November 2015 for use in patients with metastatic RCC who progressed on an angiogenesis inhibitor. Nivolumab also has an FDA-approved RCC indication in the frontline setting for patients with metastatic RCC who progressed on abiraterone (Zytiga) or enzalutamide (Xtandi).6

REFERENCES

MD Anderson and UroGen Pharma collaborate on NMIBC immunotherapy
The University of Texas MD Anderson Cancer Center announced that it has entered into an agreement with UroGen Pharma to study the novel combinatorial intravesical immunotherapy UGN-302 as a potential treatment for patients with high-grade non–muscle-invasive bladder cancer.7
The investigational intravesical treatment UGN-302 combines the toll-like receptor 7/8 agonist UGN-201 with the anti–CTLA-4 antibody UGN-301. The treatment is delivered directly to the bladder using RTGel, a platform developed by UroGen. Under the 3-year strategic collaboration, MD Anderson and UroGen will work together on designing and carrying out clinical and nonclinical studies of UGN-302. A joint steering committee will provide oversight. Funding will be provided by UroGen.

REFERENCE

Specialty pharmacy is designated as provider of relugolix
The independent specialty pharmacy Biologies by McKesson was designated as a provider of the prostate cancer drug relugolix (Orgovox).8
In January 2021, Myovant Sciences, the developer of relugolix, officially launched the gonadotropin-releasing hormone receptor antagonist in the United States, making it available through authorized specialty distributors.
The FDA approved relugolix in December 2020 for the treatment of patients with advanced prostate cancer. The approval was based on data from the phase 3 HERO study (NCT03085995), which showed that 96.7% of patients randomized to relugolix maintained castration through 48 weeks, compared with 88.8% of patients receiving leuprolide (P < .001).9
In a news release, Biologies by McKesson noted that physicians can submit prescriptions for relugolix pharmacy via phone, fax, or electronic prescription.

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ADT does not lower COVID-19 risk in men with prostate cancer

Jason M. Broderick
Associate Editorial Director, Urology Times®

Androgen-deprivation therapy (ADT) is unlikely to reduce the risk of coronavirus disease 2019 (COVID-19) infection in men with prostate cancer, according to a cohort study published in the Journal of Urology.1

The analysis included nearly 1800 men with prostate cancer from a prospective registry of men tested for COVID-19. Using multivariable analysis, the investigators found that the risk of COVID-19 infection was the same, regardless of whether the patient had received ADT (odds ratio [OR], 0.93; P = .8).

The study contradicts an Italian study published in 2020 that suggested that men with prostate cancer treated with ADT had a significantly reduced likelihood of COVID-19 infection than men not treated with ADT.2

“Androgen deprivation therapy does not appear to be protective against COVID-19 infection,” the authors wrote.

Overall, the study population comprised 1779 men with prostate cancer, of whom 5.7% (102 patients) tested positive for COVID-19 and 17.1% (304 patients) were receiving ADT. Among the ADT subgroup, 5.6% of patients were COVID-19 positive. This compared with 5.8% among patients not receiving ADT.

Patient characteristics showed that men receiving ADT were more likely to have smoked (68.1% vs 39.3% among patients not receiving ADT; P = .005), were older (75.5 vs 73.8 years, respectively; P = .009), and were more likely to have taken steroids (43.8% vs 23.3%, respectively; P < .001).

The investigators also noted that additional factors linked to a higher risk of COVID-19 infection/severity were equally distributed between the ADT group and those not receiving ADT. These included asthma, heart failure, immune suppressive disease, diabetes mellitus, hypertension, and coronary artery disease.

In the previously reported study, use of ADT in patients with prostate cancer was associated with a significantly decreased risk of contracting COVID-19 both compared with men not receiving ADT (OR, 4.05), as well as compared with patients who had any other cancer type (OR, 4.86).

The Italian investigators developed a potential explanation for this apparent “protective” effect of ADT based on TMPRSS2, an androgen regulated cofactor for COVID-19 cell entry. The investigators hypothesized that the downregulation of TMPRSS2 by ADT may protect the patient against COVID-19 infection.

However, the study published in the Journal of Urology did not corroborate this theory. “In men with prostate cancer ADT did not protect against SARS-CoV-2 infection. These results do not confirm the experience in Northern Italy. Routine use of ADT in patients at risk for or affected by COVID-19 is not warranted in the absence of controlled clinical trials showing benefits for prevention, mitigation of disease severity or improved survival. We eagerly await the results of ongoing trials testing antiandrogen agents in various stages of this disease,” the authors wrote in their conclusion.1

REFERENCES

Prostate cancer–related suicide has declined over the past 20 years

Jason M. Broderick
Associate Editorial Director, Urology Times®

Prostate cancer–related suicide decreased during the past 2 decades, according to an American Cancer Society (ACS) study published in the Journal of the National Cancer Institute.1,2

The study assessed overall trends in cancer-related suicide and determined that across all tumor types, there was a 2.8% decline per year in cancer-related suicide. In prostate cancer specifically, there was a 5.1% decline per year.

The ACS investigators, led by Xuesong Han, PhD, senior principal scientist, Health Services Research, reviewed data from the Centers for Disease Control and Prevention’s Multiple Cause of Death database, 1999-2018. The database compiles information based on death certificates for US residents. Each death certificate provides “a single underlying cause of death, up to 20 additional multiple causes, and demographic data.”

Overall, 738,743 suicides occurred during the 2-decade time frame, 6487 (0.9%) of which were determined to be cancer related. The most common cancer types among these suicides were lung and bronchus (18.2%), prostate (15.4%), colon and rectum (9.1%), lymphoma and leukemia (7.4%), and head and neck (6.7%).

Among patients with lung and bronchus, lymphoma and leukemia, and head and neck tumors, cancer-related suicides declined 4.7%, 2.6%, and 3.7%, respectively.

There were also large declines in suicide rates among individuals who were aged 65 to 74 years (~3%), aged 75 to 84 years (~3%), male (~3%), and living in urban areas (~3%).

The investigators also assessed overall suicide rates over the same 20-year period. In contrast with the decline in cancer–related suicides, the overall suicide rate increase by 1.7% per year. There were significant increases across most subgroups, including all age groups 75 years or younger, male and female individuals, all census regions, urban areas, and rural areas.1

REFERENCES
Genetic variants are linked to risk of prostate cancer

Investigators have identified nearly 90 new variants

Jason M. Broderick
Associate Editorial Director, Urology Times®

A transancestry genome-wide association meta-analysis of prostate cancer identified 86 new genetic risk variants independently associated with prostate cancer risk, according to findings published in *Nature Genetics*.1,2

The investigators also found evidence supporting the role of germline variation in health care disparities related to prostate cancer. According to the analysis, the risk of developing prostate cancer inherited by men of African ancestry is approximately twice the risk inherited by men of European ancestry. The results also showed that men of Asian ancestry inherit approximately three-fourths the risk of prostate cancer as the risk inherited by men of European ancestry.

“We not only found new markers of risk but also demonstrated that, by combining genetic information across populations, we were able to identify a risk profile that can be applied across populations,” corresponding author Christopher Haiman, ScD, professor of preventive medicine at the Keck School of Medicine of USC and director of the USC Center for Genetic Epidemiology, said in a news release.1 “This emphasizes the value of adding multiple racial and ethnic populations into genetic studies.”

Investigators at the USC Center for Genetic Epidemiology and the Institute of Cancer Research in London, England, launched this study to better understand and address disparities related to prostate cancer. According to the investigators, “We not only found new markers of risk but also demonstrated that, by combining genetic information across populations, we were able to identify a risk profile that can be applied across populations.”

Looking ahead, Haiman said, “Our long-term objective is to develop a genetic risk score that can be used to determine a man’s risk of developing prostate cancer. Men at higher risk may benefit from earlier and more frequent screening, so the disease can be identified when it’s more treatable.”

The investigators believe a large-scale clinical trial would now be needed to examine how genetic risk score could contribute to better screening/early detection.

“Most important, unlike previous screening trials, this one would need to be more representative of the diversity we see in the world,” Haiman said. “No population should get left behind.”

REFERENCES
Focal radiation boost improves outcomes in men with localized prostate cancer

Jason M. Broderick
Associate Editorial Director, Urology Times®

Adding an extra dose of external-beam radiation therapy (EBRT) to the standard EBRT improved biochemical disease-free survival (bDFS) in patients with localized prostate cancer, according to findings from the phase 3 FLAME study (NCT01684479) published in the Journal of Clinical Oncology.1,2

The focal boost was delivered directly to the intraprostatic lesion visible on multiparametric magnetic resonance imaging (mpMRI). At 5 years, the bDFS rate was 92% with the focal boost compared with 85% with standard EBRT alone (HR, 0.45; P < .001).

The added bDFS came without negatively affecting safety and quality of life. The cumulative incidence of late genitourinary toxicity grade 2 or greater was 23% with standard treatment versus 28% with the focal boost. The cumulative incidence of late gastrointestinal toxicity grade 2 or greater was 12% versus 13%, respectively. Also, there were only small, statistically insignificant differences in health-related quality of life between the 2 arms.

“The radiation boost halved the percentage of men presenting with raised PSA levels over the first 5 years after treatment: from 15% to 8%,” radiation oncologist and research leader Linda Kerkmeijer, MD, PhD, of UMCG Utrecht and Radboudumc, said in a news release. “The radiation boost did not lead to additional side effects, which is an important outcome.”

Between 2009 and 2015, the single-blind FLAME (Focal Lesion Ablative Microboost in Prostate Cancer) study enrolled 571 men with localized intermediate- or high-risk prostate cancer. Patient characteristics were well balanced between the 2 study arms. Across the overall population, the mean age was 70 years.

Patients were randomized in a 1:1 ratio to receive standard treatment alone (n = 287) or standard treatment plus the focal boost (n = 284). Standard treatment was conventionally fractionated EBRT comprising 77 Gy in 35 fractions of 2.2 Gy to the entire prostate.

The additional radiation in the experimental arm consisted of a simultaneously delivered integrated focal boost to the macroscopic tumor as visible on mpMRI. The boost was up to 95 Gy, comprising 35 fractions of up to 2.7 Gy. If necessary, investigators reduced the boost to comply with prespecified organs at risk constraints.

The median follow-up time was 72 months. Five-year bDFS was the primary end point. Secondary end points consisted of DFS, distant metastases–free survival, prostate cancer–specific survival, overall survival, toxicity, and health-related quality of life.2

REFERENCES

Letters

We welcome letters to the editor. Please send correspondence to urology_times@mmhgroup.com.

Medicare covers annual PSA-based screening

To the editor:

In the early 1990s, the annual prostate-specific antigen (PSA) screening test for men 50 years and older reduced prostate cancer (PCa) mortality by 50%. Unfortunately, in 2012, based on a flawed PCa screening trial (Screening for Prostate Cancer in Older Patients [PLCO Screening Trial], NCT00002540), the United States Preventive Services Task Force (USPSTF) recommended against PCa screening. By 2018, the USPSTF upgraded the recommendation for PSA-based PCa screening from grade D to C (but maintained a grade D for men 70 years and older). These recommendations are largely followed by frontline primary care physicians, and currently 50% of primary care doctors are not offering their patients annual PCa screening. The US data indicate that the lack of PCa screening has increased the number of patients with PCa, PCa metastasis, and PCa mortality, especially in men 70 years and older. The American Cancer Society reported 161,360 new cases of PCa and 26,730 deaths due to PCa in 2017 compared with 191,930 new cases and 33,330 deaths in 2020, respectively. In 2010, Medicare spent $11.8 billion on PCa treatment which increased to 15.3 billion by 2018, largely because of treatment of advanced PCa.

As PCa specialists, we have reviewed our local experience with PCa and have published our results in US urology peer-reviewed journals (7 papers and 13 letters). Our most recent paper, “A Trend Toward Aggressive Prostate Cancer,” showed that the number of prostate biopsies have decreased by 45% while the diagnosis of PCa has increased 3-fold. Our data (and other US data) have highlighted 3 high-risk groups for PCa—African American (AA) men, men with a family history of PCa and healthy men age 70 and above.

The PLCO PCa screening randomized trial on which the USPSTF based its recommendations against PSA-based PCa screening was contaminat-ed (90% of the men in the nonscreening arm were screened) and had only 4% AA men. In the US, AA men represent about 12% of the population and in large cities represent over 30%. Based on our data and that of other US groups, we strongly believe that annual PCa screening (PSA and digital rectal exam) should be offered to all men 55 years and older. PCa screening should especially be offered to high-risk men—AA men, men with a family history of PCa, and healthy men 70 years and older. Currently, due to enhanced risk assessment tools (both MRI imaging and genetic tests) and the ability to offer men active surveillance, overtreatment of PCa has been significantly reduced.

According to current Medicare policy, Medicare covers an annual PSA-based PCa screening for men 50 years and older. Our goal is to highlight this coverage policy so that PSA-based PCa screening can be increased to diagnose and cure early PCa, thereby reducing PCa morbidity, mortality, and cost associated with late-stage treatment.

Navin Shah, MD; and Vladimir Ioffe, MD / Greenbelt, Maryland

REFERENCE

Prostate Cancer / CLINICAL UPDATES
Enzalutamide plus ADT improves PFS in men with bone and/or lymph node metastases

Limited benefits are seen in patients with prostate cancer and liver metastases, however

According to Armstrong, the limited benefits in men with liver metastases suggest that it may be less androgen receptor dependent, which calls for new strategies to understand this pattern of spread at the molecular level to reduce death and negative experiences from prostate cancer.

“Liver metastases were already known to be associated with a poor prognosis in metastatic castration-resistant prostate cancer, but our data add to this importance in earlier disease settings,” he said.

For now, urologists and oncologists should consider a liver biopsy to evaluate for neuroendocrine or small cell prostate cancer as per National Comprehensive Cancer Network and American Urological Association guidelines, Armstrong said.

“Such men are more likely to benefit from docetaxel and ADT in this setting, given the results of the CHARTED [NCT03009985] and STAMPEDE [NCT00268476],” he said.

Radiographic PFS is a clinically relevant end point that urologists and other physicians use to make treatment decisions that impact patients’ lives in practice, Armstrong said.

There are major treatment implications when a patient with metastatic hormone-sensitive prostate cancer progresses to metastatic castration-resistant prostate cancer, requiring changes to strategies, given the abundance of approved agents in the metastatic castration-resistant prostate cancer setting.

According to Armstrong, with the improvements in radiographic PFS observed in ARCHES, the FDA approved enzalutamide in the metastatic hormone-sensitive prostate cancer setting.

“Patients were offered cross-over and open-label access to enzalutamide,” he said. “Enzalutamide is known to improve survival in castrate-resistant prostate cancer patients already, and continuing this study to a survival primary endpoint was not reasonable given the results of the ENZAMET trial [NCT02446405], which demonstrated improved survival with enzalutamide in this setting.”

According to Armstrong, there are downsides to adding the androgen receptor inhibitor to treatment. Enzalutamide adds adverse events (AEs) to ADT alone, including fatigue, high blood pressure, loss of bone density, fracture risks, muscle loss, fall risk, and hot flushes. Some men experience cognitive issues with fatigue. Providers can help patients reduce these AEs through attention to exercise, bone health, cardiovascular risk factors, and blood pressure monitoring.

The work to find optimal treatments for these patients is far from over.

“Although enzalutamide, abiraterone, and apalutamide each extend life in men with metastatic hormone-sensitive prostate cancer, these patients still progress after several years of treatment, and new therapies are needed,” Armstrong said. “Men with liver metastases progress the fastest, and this group represents the largest unmet medical need [for] research to understand how prostate cancers favor the liver microenvironment and how we can improve survival in this setting and prevent liver metastases.”

Future studies, he said, will examine whether enzalutamide and ADT after completion of docetaxel and ADT in these patients with poor-prognosis, visceral metastatic hormone-sensitive prostate cancer can extend survival.

For now, men with metastatic hormone-sensitive prostate cancer should be educated about their prognosis based on their disease risk and pattern of spread, Armstrong said.

Disclosure: Astellas Pharma and Pfizer funded the study. Andraz Armstrong, MD, is a consultant with Astellas, Pfizer, Bayer, and Janssen.

REFERENCE
XTANDI is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC) or metastatic castration-sensitive prostate cancer (mCSPC).

No need to wait. START XTANDI.

Importantly, the first and only oral treatment approved by the FDA in 3 advanced prostate cancer patient types—mCSPC, nmCRPC, and mCRPC.

**Important Safety Information**

**Warnings and Precautions**

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)** There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

**Hypersensitivity** reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in seven randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

**Ischemic Heart Disease** In the combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs. 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on XTANDI versus 0.7% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

**Falls and Fractures** occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo.

**Embryo-Fetal Toxicity** The safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

**Adverse Reactions (ARs)** In the data from the four randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 2% over placebo) in XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. In the bicalutamide-controlled
XTANDI significantly extended metastasis-free survival\(^1\) and overall survival\(^2\) in patients with nmCRPC\(^1\)

**PROSPER** was a multinational, randomized, double-blind, placebo-controlled phase 3 study in 1401 patients with nmCRPC who had progressed\(^6\) on LHRH therapy\(^8\). Overall survival data were updated in the final analysis\(^3\).

### METASTASIS-FREE SURVIVAL (PRIMARY ENDPOINT)

- **71%** reduction in the risk of metastasis or death with XTANDI + LHRH therapy\(^8\) vs placebo + LHRH therapy\(^4\) (HR = 0.29 [95% CI, 0.24-0.35]; P < 0.0001)\(^1\)

### OVERALL SURVIVAL (SECONDARY ENDPOINT)

- **27%** reduction in the risk of death with XTANDI + LHRH therapy\(^8\) vs placebo + LHRH therapy\(^4\) (HR = 0.73 [95% CI, 0.61-0.88]; P = 0.0011)\(^3\)

**Permitted at baseline:** Patients with prior anti-androgen therapy with a 4-week washout period to randomization. Bicalutamide treatment prior to randomization was received by 55% and 58% of patients in the XTANDI and placebo arms, respectively.\(^4,5\)

**Key eligibility criteria included** nmCRPC (central review), > 3 rising PSA values despite castrate testosterone levels (< 50 ng/dL), \(^1\) baseline PSA > 2 ng/mL, PSADT ≤ 10 months, no prior chemotherapy, ECOG Performance Status of 0 or 1.\(^1,5,6\)

**Exclusion criteria included** prior abiraterone acetate use, history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, or clinically significant cardiovascular disease.\(^4\)

The primary endpoint of the study was **metastasis-free survival**, defined as the time from randomization to whichever of the following occurred first: 1) local-regional and/or distant radiographic progression per blinded independent central review; or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression.\(^1\)

Overall survival was measured as the interval from randomization to death from any cause.\(^1\)

**Progression** was defined as at least 3 rising PSA values (PSA1 < PSA2 < PSA3) taken at least 1 week apart despite castrate levels of testosterone (< 50 ng/dL) on LHRH therapy or after bilateral orchiectomy.\(^1\)

\(^1\)For after bilateral orchiectomy.

### Drug Interactions

**Effect of Other Drugs on XTANDI**

Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

**Effect of XTANDI on Other Drugs**

Avoid CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

**Data on File.**

**References:**


Please see adjacent pages for Brief Summary of Full Prescribing Information.

For more information, please visit [XtandiHCP.com](http://XtandiHCP.com)

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XTANDI® (enzalutamide) tablets, for oral use

XTANDI® (enzalutamide) capsules for oral use

fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls and Fractures

falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or fracture. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS and PRECAUTIONS reflect seven randomized, placebo-controlled trials (AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, Asian PREVAIL, and STRIVE) that were pooled to conduct safety analyses in patients with CRPC (N=3509) or mCSPC (N=5727) treated with XTANDI. Patients received XTANDI 180 mg (N=4081 patients) or placebo orally once daily (N=2472 patients) or bicalutamide 50 mg orally once daily (N=3497 patients). All patients continued androgen deprivation therapy (ADT). In these seven trials, the median duration of treatment was 13.6 months (range: <0.1 to 87.6) in the XTANDI group.

In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the median duration of treatment was 14.3 months (range: <0.1 to 87.6) in the XTANDI group. In these four trials, the most common adverse reactions (≥10%) that occurred more frequently (≥2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension.

AFFIRM (NCT00974311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events were reported for 18% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥2% higher frequency in the XTANDI arm compared to the placebo arm.

<table>
<thead>
<tr>
<th>Table 1. Adverse Reactions in AFFIRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XTANDI</strong></td>
</tr>
<tr>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
</tr>
<tr>
<td>Asthenic Conditions</td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
</tr>
<tr>
<td>Musculoskeletal Injuries</td>
</tr>
<tr>
<td>Dermatological Disorders</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vascular Disorders</td>
</tr>
<tr>
<td>Hot Flush</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Neurological Disorders</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Nausea, Vomiting, and Cauda Equina Syndrome</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Mental Impairment Disorders*</td>
</tr>
<tr>
<td>Appendicitis</td>
</tr>
</tbody>
</table>

In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or fracture. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.
<table>
<thead>
<tr>
<th>Table 1. Adverse Reactions in AFFIRM (cont’d)</th>
<th>XTANDI (N = 860)</th>
<th>Placebo (N = 844)</th>
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<tbody>
<tr>
<td>General Disorders</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td>Peripheral Edema</td>
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<td>2</td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td>3</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Vascular Disorders</td>
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<tr>
<td>Hepatitis</td>
<td>14</td>
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<tr>
<td>Nervous System Disorders</td>
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<td>Insomnia</td>
<td>11</td>
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<tr>
<td>Major Organ Malignancy</td>
<td>7</td>
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<tr>
<td>Nerve Root Compression</td>
<td>0.1</td>
<td>0.1</td>
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<td>Respiratory Disorders</td>
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<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Infections and Metastasis</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Urinary Tract Dysfunction</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>4</td>
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<tr>
<td>Respiratory Failure</td>
<td>4</td>
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<tr>
<td>Nervous System Disorders</td>
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<tr>
<td>Insomnia</td>
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<td>11</td>
</tr>
<tr>
<td>Major Organ Malignancy</td>
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<td>7</td>
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<tr>
<td>Nerve Root Compression</td>
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<td>0.1</td>
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<td>Respiratory Disorders</td>
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<td>Dyspnea</td>
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<td>1</td>
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<tr>
<td>Infections and Metastasis</td>
<td>0.5</td>
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<tr>
<td>Urinary Tract Dysfunction</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2. Adverse Reactions in PREVAIL (cont’d)</th>
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<th>Placebo (N = 1836)</th>
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</thead>
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<td>General Disorders</td>
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<td>Grade 3-4 (%)</td>
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<td>Asthenic Condition</td>
<td>185</td>
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<td>Peripheral Edema</td>
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<td>18</td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>22</td>
<td>22</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Diarrhea</td>
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<td>32</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>21</td>
<td>21</td>
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<tr>
<td>Hepatitis</td>
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<tr>
<td>Nervous System Disorders</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Major Organ Malignancy</td>
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<td>38</td>
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<tr>
<td>Nerve Root Compression</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infections and Metastasis</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Urinary Tract Dysfunction</td>
<td>0.5</td>
<td>0.5</td>
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<table>
<thead>
<tr>
<th>Table 3. Adverse Reactions in TERRAIN</th>
<th>XTANDI (N = 1395)</th>
<th>Bicalutamide (N = 1395)</th>
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</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Asthenic Condition</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>29</td>
<td>29</td>
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<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
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</tr>
<tr>
<td>Vascular Disorders</td>
<td>36</td>
<td>36</td>
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<tr>
<td>Hepatitis</td>
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<tr>
<td>Nervous System Disorders</td>
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<td>23</td>
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<tr>
<td>Insomnia</td>
<td>17</td>
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<td>Major Organ Malignancy</td>
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<td>25</td>
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<tr>
<td>Nerve Root Compression</td>
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<tr>
<td>Respiratory Disorders</td>
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<tr>
<td>Dyspnea</td>
<td>3</td>
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</tr>
<tr>
<td>Infections and Metastasis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinary Tract Dysfunction</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>
Table 5 shows adverse reactions reported in ARCHES that occurred at a
received XTANDI. Fatigue/asthenia was the most frequent adverse reaction
were arthralgia, and fatigue, each in 0.3%. Discontinuation in XTANDI-treated patients were alanine aminotransferase increased,
the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of
patients treated with XTANDI. Permanent discontinuation due to adverse events as
and sudden death (n=2). Grade 3 or higher adverse events were reported in 24% of
months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo.
ARCHES (NCT02677896): XTANDI versus Placebo in Metastatic CSPC Patients
≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XTANDI</th>
<th>Placebo</th>
<th>XTANDI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[N=572]</td>
<td>[N=574]</td>
<td>[N=930]</td>
<td>[N=932]</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Decreased Appetite</td>
<td>9.6</td>
<td>0.2</td>
<td>3.9</td>
<td>0.2</td>
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<tr>
<td>Nervous System Disorders</td>
<td>12</td>
<td>0.5</td>
<td>3.2</td>
<td>3.2</td>
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<tr>
<td>Headache</td>
<td>9.1</td>
<td>0.2</td>
<td>4.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Cognitive And Attention Disorders</td>
<td>4.6</td>
<td>0.1</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
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<td>0.1</td>
<td>7.4</td>
<td>5.0</td>
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<tr>
<td>Hypertension</td>
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<td>0.1</td>
<td>5.2</td>
<td>2.2</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<td>8.6</td>
<td>0.6</td>
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<tr>
<td>Nausea</td>
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<td>0.2</td>
<td>8.4</td>
<td>0.4</td>
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<tr>
<td>Hematologic Disorders</td>
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<td>0.4</td>
<td>0.0</td>
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<tr>
<td>Anemia</td>
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<td>0.9</td>
<td>0.2</td>
<td>0.4</td>
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<tr>
<td>Platelet Decreased</td>
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<td>0.0</td>
<td>0.4</td>
<td>0.0</td>
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<td>Injury, Poisoning and Procedures Complications</td>
<td></td>
<td></td>
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<tr>
<td>Fractures*</td>
<td>9.0</td>
<td>0.2</td>
<td>4.9</td>
<td>1.7</td>
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<td>Psychiatric Disorders</td>
<td>2.8</td>
<td>0.2</td>
<td>1.1</td>
<td>0.0</td>
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</table>

Laboratory Abnormalities
Table 6 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 6. Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XTANDI</th>
<th>Placebo</th>
<th>XTANDI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[N=3173]</td>
<td>[N=2282]</td>
<td>[N=3173]</td>
<td>[N=2282]</td>
</tr>
<tr>
<td>Hematopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>0.9</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>WHITE blood cell decreased</td>
<td>17</td>
<td>0.4</td>
<td>9.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Hematology</td>
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<tr>
<td>Hemoglobin</td>
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<td>75</td>
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<td>Hypercalcemia</td>
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<td>Hypertension</td>
<td>1.4</td>
<td>0.9</td>
<td>8.6</td>
<td>1.9</td>
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</table>

Hypertension
In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience
The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting
Immune System Disorders: hypersensitivity
Musculoskeletal Disorders: posterior reversible encephalopathy syndrome (PRES)
Neurological Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)).

DRUG INTERACTIONS

Drugs that inhibit CYP3A4
Co-administration of a strong CYP3A4 inhibitor (fentanyl) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP3A4 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP3A4 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that increase CYP3A4
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, diltiazem, ergotamine, fentanyl, imatinib, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose (see Data).
In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased antenatal and postnatal growth at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the milk of lactating rats (see Data). Data following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a Cmax that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

Females and Males of Reproductive Potential

Contraception
Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI.

Infertility
Males
Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use
Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use
Of 4081 patients who received XTANDI in seven randomized, controlled clinical trials, 78% were 65 and over, while 35% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment
A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min < creatinine clearance (CrCL) ≤ 60 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment
Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

OVERDOSE
In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.
Prostate Cancer / COVER FEATURE

EMMANUEL S. ANTONARAKIS, MD

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PARP INHIBITORS

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amount of DNA damage in the cancer cell. As a general principle, a little bit of DNA damage is a good thing for a cancer cell; it helps it survive and metastasize and grow more rapidly and proliferate. But too much DNA damage can be a bad thing because it can lead to catastrophic genomic instability and subsequent cancer cell death.

PARP inhibitors work best in cancers that have mutations in homologous recombination repair (HRR) genes. The most well known of these in prostate cancer is BRCA2. BRCA2 is a gene (and a protein) that is responsible for fixing double-strand DNA breaks. There is another way that cancer cells can fix DNA breaks, which is called single-strand repair, fixing 1 DNA strand at a time. So if you have a patient with a BRCA2 mutation, that cancer cell's ability to fix double-strand DNA breaks is impaired. It then relies on the other pathway, the single-strand repair pathway, to fix its DNA damage. That single-strand repair pathway is done by an enzyme called PARP, primarily PARP1. If PARP1 is inhibited by a drug, such as a PARP inhibitor, in a patient who already has a mutation in the alternative mechanism of DNA repair—in other words, BRCA2—that then cancer cell develops catastrophic DNA damage, so that the next time it replicates it's not able to survive and it dies.

Again, this concept is synthetic lethality. It simply means that you need a one-two punch to kill the cancer cells. The first punch comes from the genetic mutation that the cancer has, and the second punch comes from the PARP inhibitor, leading to catastrophic DNA damage in the cancer cell and subsequent cell death.

Q: Please discuss the key findings from the TRITON2 (NCT02952534) and PROfound (NCT02987543) clinical trials of rucaparib and olaparib.

A: In May 2020, there were 2 FDA approvals for PARP inhibitors in prostate cancer within 5 days. The first was rucaparib, a PARP inhibitor approved based on a phase 2 single-arm study without a control group, called TRITON2. The TRITON2 study, in an unprecedented way, led to FDA approval of a drug in prostate cancer without requiring randomization and without having a control group. However, it was an accelerated FDA approval, meaning that full approval by the FDA is contingent upon a positive phase 3 randomized study (TRITON3 [NCT02975934]), which is ongoing.

TRITON2 evaluated patients who had 1 or more DNA repair gene mutations. The 2 genes of greatest interest were BRCA1 and BRCA2, and there were a handful of other, more rare genes included as well. Patients had to have either germline mutations within 1 of those genes, or somatic mutations in a tumor in 1 of those genes. They then received rucaparib twice daily. The primary end point of the study was not overall survival (OS) or progression-free survival (PFS) like other studies that we have seen, but rather the objective response rate. A secondary end point was the prostate-specific antigen (PSA) response rate. Approximately 40% of patients with a BRCA1 or BRCA2 mutation who received rucaparib had an objective response, and the PSA response rate was even higher at about 50%. The efficacy in the other non-BRCA genes was less impressive, and FDA approval was not sought for any of the other genes. Thus, the accelerated approval for rucaparib, granted in May 2020, was only for patients with germline or somatic BRCA1 or BRCA2 mutations. The other small but important point is that the TRITON2 study required patients to have metastatic castration-resistant prostate cancer, and they had to have disease progression despite previously receiving at least 1 novel hormone therapy and 1 chemotherapy. The accelerated FDA approval reflected that patient population, meaning that patients who are eligible to receive this drug (now that it has been approved) should have previously received both a novel hormone agent plus a chemotherapuy agent.

The second trial, which was the PROfound study, led to the full FDA approval of olaparib. This was a phase 3 randomized study for patients with a genetic mutation in BRCA1, BRCA2, ATM, or 12 other genes. The primary end point of interest was radiographic PFS for patients with either BRCA1, BRCA2, or ATM mutations. A key secondary end point was OS in this cohort. Patients with metastatic castration-resistant prostate cancer who had received at least 1 novel hormone therapy, plus up to 1 chemotherapy (although the chemotherapy was not mandated), were randomized to receive either olaparib or a physician's choice of hormonal therapy. The trial was positive, showing a significant prolongation of radiographic PFS but also OS in the patients who had BRCA1, BRCA2, and ATM mutations.

As a prespecified secondary analysis, the trial was also powered to evaluate the overall patient population that included patients with mutations in any of the 15 HRR genes, not just the 3 mentioned above. In that entire study population, there was also a prolongation of radiographic PFS with olaparib compared with placebo. This led the FDA to approve olaparib for not just the BRCA1, BRCA2, and ATM genes, but also various other HRR genes, including CHEK2, PALB2, CDK12, and several others.

Q: What genetic testing is needed to determine a patient's eligibility for treatment with a PARP inhibitor?

A: Patients with prostate cancer who are eligible for treatment with a PARP inhibitor have to have either a germline or somatic mutation in 1 or more of the DNA repair genes. In the case of olaparib, the range of genes is more expansive and includes 14 genes, including but not limited to BRCA1, BRCA2, ATM, CHEK2, PALB2, and CDK12. There are a few others as well.

However, in the case of rucaparib, the treatment is restricted to patients who have either germline or somatic BRCA1 or BRCA2 mutations only. At this time, rucaparib cannot be recommended for...
patients with non-**BRCA2** mutations.

Germline genetic tests can be done using saliva or peripheral blood leukocytes. Somatic genetic testing requires a tumor sample, either a metastatic tumor biopsy or an archival primary prostatic biopsy. In addition, there are now several commercial circulating tumor DNA assays that can assess tumor DNA using a blood test.

**Q:** How will urologists be involved with the administration of PARP inhibitors?

**A:** In general, the prescriptions of these agents will mostly be coming from medical oncologists. However, urologists do have an important role in identifying patients for potential eligibility for PARP inhibitors down the line; for example, patients with germline mutations in **BRCA2** will become eligible for PARP inhibitor treatment if they eventually develop metastatic castration-resistant disease. Unlike somatic genetic testing, which is currently only recommended in the National Comprehensive Cancer Network guidelines for patients with metastatic disease, germline testing is recommended for patients with nonmetastatic prostate cancer as well; for example, if they have intermediate- or high-risk localized prostate cancer, if they have any type of localized prostate cancer with a family history of prostate, breast, or ovarian cancers, or if they have an ancestral Ashkenazi Jewish background.

If patients who don’t yet have metastatic or castration-resistant prostate cancer are identified by a urologist as having a germline mutation in a gene such as **BRCA2,** then those patients could be prioritized prospectively for future treatment with a PARP inhibitor as soon as they become eligible, rather than trying to scramble and get a biopsy of metastatic tissue after the patient has already developed castration-resistant prostate cancer, where some time may be lost in planning for PARP inhibitor treatment.

The other interesting thing is we are now seeing studies evolving in the neoadjuvant space and adjuvant space, where PARP inhibitors are being investigated in an experimental fashion for patients who have mutations in one of these **HRR** genes. So it is likely that several urologists across the country may have access to one of these neoadjuvant or adjuvant or early biochemical recurrence studies that are incorporating a PARP inhibitor in an investigational fashion for patients with prostate cancer harboring germline or somatic **HRR** mutations.

**Q:** What adverse events (AEs) should urologists be particularly mindful of when a patient receives a PARP inhibitor, and how are these effects optimally managed?

**A:** The AEs of PARP inhibitors are broadly similar and overlapping. They include fatigue, nausea, anorexia, and suppression of blood counts, especially platelets and white blood cells. Fatigue is usually self-limiting and does not require intervention, although sometimes a dose reduction may be needed. Anemia, in most cases, is also relatively asymptomatic, although in some patients, it can result in fatigue or dyspnea, or other clinical symptoms. In about 15% of patients, anemia can be severe enough to warrant a red blood cell transfusion. We also need to keep a close eye on the renal function of patients, especially creatinine level, because these drugs, as a class, can cause an elevation of creatinine.

There is 1 AE that is specific to olaparib that does not appear to be present with rucaparib, and that is a dry cough. Olaparib is associated with a cough in about 5% of patients. The cough disappears when the drug is stopped and often reappears if the drug is introduced again, even in a lower dose. Also, there have been case reports of a rare but serious pneumonitis (inflammation of the lung), which again can rarely occur with olaparib, but has not been seen yet with rucaparib. Olaparib may also be associated with a slight predisposition to venous thromboembolic complications, such as deep vein thrombosis and pulmonary embolism.

Finally, these drugs all have a theoretical and real (but small) risk of either accelerating or inducing myelodysplastic syndromes and potentially even acute myeloid leukemia. In patients who are older and already have preexisting myelodysplasia, these drugs should probably be avoided. If there is any evidence of a myelodysplastic syndrome, these patients should see a hematologist who specializes in myelodysplasia and should discontinue PARP inhibitor treatment.

**Q:** Can you discuss the next steps for PARP inhibitors and prostate cancer, including combination therapy trials of PARP inhibitors with immunotherapies or androgen receptor (AR) pathway inhibitors?

**A:** There are at least 2 future directions for these agents with other standard therapies for metastatic prostate cancer. We have been using drugs such as abiraterone acetate (Zytiga) and enzalutamide (Xtandi) for almost a decade now. These are natural combination partners with PARP inhibitors. There are a number of pivotal phase 3 studies that could lead to FDA approval of these combinations. For example, there is TALAPRO-2 (NCT03995197), a phase 3 randomized study of talazoparib plus enzalutamide versus enzalutamide alone in patients with metastatic castration-resistant prostate cancer.

In addition, there is also the MAGNITUDE (NCT03748641) trial, a phase 3 randomized study evaluating niraparib plus abiraterone in patients with metastatic castration-resistant prostate cancer. The goal of those studies is to see whether the combination of a PARP inhibitor and a novel hormonal therapy might be successful in genetically unselected patients; in other words, not just patients who might have one of these **HRR** gene mutations.

PARP inhibitors are also being studied in the metastatic hormone-sensitive setting. The recently launched AMPLITUDE trial (NCT04497844) is a phase 3 randomized study evaluating niraparib plus abiraterone in patients with metastatic castration-resistant prostate cancer. The goal of those studies is to see whether the combination of a PARP inhibitor and a novel hormonal therapy might be successful in genetically unselected patients; in other words, not just patients who might have one of these **HRR** gene mutations.

The second future direction is the combination of PARP inhibitors with immunotherapies, such as PD-1 inhibitors. There are a number of phase 3 studies that either are being designed

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**REFERENCE**

Facility volume is linked with survival for men with node-positive prostate cancer

Hannah Slater
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Patients with node-positive (N1) prostate cancer receiving radiation plus androgen deprivation therapy (ADT) had improved overall survival (OS) if they were treated at a high-volume facility, according to a study published in jAMA Network Open.1

The facilities assessed in the study were high-volume radiation centers (regardless of academic affiliation), and the investigators were specifically observing outcomes in patients who received external beam radiation therapy (EBRT) with concomitant ADT.

“Numerous studies have shown that patients with cancer who are treated at high-volume facilities have higher rates of long-term survival, including those who undergo primary surgery, radiation, or chemotherapy,” wrote the study authors, led by Sagar A. Patel, MD, of Emory University School of Medicine in Atlanta, Georgia. “Given the complexity of management of N1 prostate cancer, we hypothesized that men treated at high-volume centers would have improved OS compared with those treated at low-volume centers.”

The cohort study assessed men with a diagnosis of T1N1M0 to T4N1M0 prostate cancer treated with curative-intent EBRT and ADT between January 2004 and December 2016 at facilities in the United States reporting to the National Cancer Database. Overall, 1899 men met the inclusion criteria and were enrolled in the study.

The study defined treatment at a center with high versus low average cumulative facility volume (ACFV) as the total number of prostate radiation cases at a given treatment facility from 2004 until the year of the respective patient’s diagnosis. The ideal ACFV cutoff point was found to be 66.4 patients per year.

Among patients treated at high-ACFV centers, the median OS was 111.1 months compared with 92.3 months in low ACFV centers (P=.01). Moreover, on multivariate analysis, treatment at a center with low ACFV was associated with increased risk of death (HR, 1.22; P=.03) when compared with treatment at a center with high ACFV. Following propensity score–based adjustment, these results persisted.

The investigators noted that there are other aspects of care at high-volume centers that could explain the higher long-term survival rate observed in men with N1 prostate cancer. For example, high-volume facilities may contain optimal multidisciplinary care in the same hospital and center. Given that treatment of men with advanced prostate cancer requires close collaboration between a multitude of disciplines, it is possible that high-volume centers more often have close collaboration and workflows between these disciplines.

Further, high-volume centers might utilize advanced molecular imaging—such as fluciclovine, choline, or prostate-specific membrane antigen PET—more frequently, which may detect occult nodal disease, resulting in stage migration and better outcomes versus those who have more advanced nodal disease burden that is detectable by conventional imaging. Clinical health care providers at high-volume facilities, including advanced practitioners and nurses, might also have more experience with managing acute toxic effects typically associated with aggressive local and systemic therapy.

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or currently enrolling patients. One example is the KEYLYNK-010 (NCT03834519) study, a phase 3 randomized trial of olaparib plus pembrolizumab versus either enzalutamide or abiraterone in patients with metastatic castration-resistant prostate cancer who have received 1 novel hormonal therapy and 1 taxane chemotherapy. That study is expected to read out in 2022.

Q: Some experts have said that the approval of PARP inhibitors marks the dawn of the precision medicine era in prostate cancer. In your opinion, where does precision medicine go from here in prostate cancer treatment paradigm?

A: The modern definition of precision medicine often involves a genetic or genomic test identifying a particular mutation that then leads to a vulnerability of cancer to a particular drug. I would argue that precision medicine in prostate cancer started 50 or more years ago because the AR is one of the prototypical oncogenes that we have been targeting in this disease for a long time.

In my opinion, we have at least 2 examples of precision medicine in prostate cancer thus far, but we are still way behind other cancers such as lung and breast. The first example came in 2017 when the FDA approved pembrolizumab (Keytruda) for any patient with any cancer type with a mismatch repair gene mutation or microsatellite instability-high genotype. However, only 3% to 4% of prostate cancers have mismatch repair deficiency or microsatellite instability. A more recent example of precision medicine came in May of 2020, with the approval of rucaparib and olaparib for HRRC-mutated or BRCA1/BRCA2-mutated prostate cancer.

There are additional examples of precision medicine treatments in the pipeline. There are drugs that inhibit the AKT pathway or the PI3K pathway that might be efficacious in prostate cancers with either deletion or mutation in PTEN or with activation of PI3K or AKT pathways. One example is the drug ipatasertib (an oral AKT inhibitor), which has been tested in patients with PTEN loss and may lead to FDA approval in those patients based on the positive results of the IPATential150 (NCT03072238) trial.2

“We have been using drugs such as abiraterone acetate (Zytiga) and enzalutamide (Xtandi) for almost a decade now. These are natural combination partners with PARP inhibitors.”

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Urologists must remain vigilant regarding post-BCG infection

Intravesical instillation of BCG remains the most frequently utilized therapy against high-grade non–muscle-invasive urothelial bladder cancer (NMIBC). Treating urologists are quite familiar with the identification and management of early urinary and systemic adverse events of BCG instillation. However, the spread of BCG infection to other organs is less well appreciated. Cabas et al performed a systematic review of the published literature demonstrating the frequency and timing of potentially serious post-BCG infections involving genitourinary (GU) and non-GU sites.

To identify all case reports of post-BCG infections, the investigators systematically reviewed 401 publications through Medline and other searches. Of these, 271 case reports met the inclusion criteria for the review. From these reports, the authors compiled data including demographics, tumor grade/stage, number of intravesical instillations, number of organs with BCG infection, time from last BCG instillation to signs of infection, type of imaging utilized, microbiological confirmation, type and duration of surgical and nonsurgical treatment, and patient outcomes.

Of the 307 cases of post-BCG infection, only 4 (1.3%) occurred in female patients. The average number of intravesical BCG instillations prior to developing symptoms of infection was 8 plus or minus 5.3 instillations. A single organ/site was infected in 72.0%, 2 organs were affected in 20.2%, and 3 or more organs were affected in 7.8% of the cases. Of all the cases identified by the authors, including those with multiple organs involved, BCG-related infection of GU organs occurred in 33.7% and non-GU organs were involved in 76.2% of cases. Most frequently involved sites included non-GU organs such as lungs, vascular system, and liver, whereas the various GU organs (testis, penis, prostate, and kidneys) were involved equally and infrequently.

The median time from last BCG instillation to clinical signs of infection varied and depended on the organs involved. The granulomatous infection of the liver and lungs (such as milky pulmonary infection) occurred earlier, at a median time of 1 week from the last instillation. In contrast, vascular lesions (endograft graft infection or mycotic aneurysm), bone/joint involvement (prosthetics infection or spondylodiscitis), and muscular involvement (psoas abscesses) occurred late, at a median of 52, 68, and 93 weeks, respectively. Among the GU organs, penile lesions (erythema, ulcer, granulomatous lesions) appeared at a median of 1 week, prostatitis or abscess at 3 weeks, renal granulomatous disease at a median of 8 weeks, and epididymo-orchitis at a median of 56 weeks.

Overall, microbiological diagnosis was made in 55.6% of cases through acid-fast stain, culture, or polymerase chain reaction test. The rate of isolation and mycobacteria identification at the affected sites also appears to be related to the organs involved. Microbiological detection was noted in 28.6% of penile lesions, 35.2% of lung lesions, and nearly 60% of prostate/epididymis/testis lesions. The highest rates of microbiological detection of the mycobacteria were noted in vascular (83.6%), bone/joint (91.7%), and muscle lesions (100%). In evaluating concomitant infections at various sites, the investigators observed a strong association (P < .001) between lungs and liver complications, bone marrow and liver complications, bones/joints and muscles, and lungs and bone marrow complications.

The reported duration of antmycobacterial therapy ranged from a median of 6 weeks for penile or testicular lesions, 8 weeks for lungs or liver lesions, and 12 weeks for bone/joint infections. Surgical intervention was most frequently required for cases of infections involving vascular (83%), bone/joint (85.4%), and muscular systems (90.5%), whereas surgical intervention was relatively infrequent for lung (6.8%) and liver (8.9%) infections.

Of the GU organs involved with post-BCG infection, a majority (55%-90%) of the penile, prostate, and kidney infections manifested within 1 month of the last BCG instillation, whereas testicular infections appeared after 12 months or longer. For the non-GU organs, there appears to be a biphasic distribution of the time to post-BCG infection. A majority (50%-75%) of the lung, liver, and bone marrow infections became apparent within 1 month. More than 50% of the infections involving vascular, muscular, and bone/joint systems appeared 12 to 24 months after the last BCG instillation.

An interesting observation from this compilation of 307 case reports is that only 1.3% of post-BCG systemic infections occurred in female patients. One may speculate that the male anatomy (bulbar urethra, prostate) is more prone to catheter-related trauma during instillation, followed by increased exposure of traumatized area to the BCG when voiding. Both of these would result in potential intravasation of BCG resulting in systemic spread of BCG. Thus, strict adherence to the protocol for canceling the BCG in the presence of infection, and aborting the instillation in the setting of trauma and/or any degree of gross hematuria, is required. Although systemic infections involving non-GU organs are uncommon, these infections are associated with significant morbidity, and mortality. Of the 65 cases of vascular involvement, 10 (15.4%) died of BCG-related complications. The mortality rate for the post-BCG infections involving lungs, liver, and muscles was reported to be 4.1%, 3.6%, and 4.8%, respectively.

This study provides useful data on the frequency and timing of BCG-related infection of various organ systems. Urologists play a pivotal, long-term role in the diagnosis and treatment of NMIBC, and essentially serve as the primary oncologists for patients with NMIBC. It is essential for us to be vigilant about all the complications, whether local or systemic, associated with intravesical BCG. A high index of suspicion is required for early identification of these infections, but potentially lethal, post-BCG systemic infections.

REFERENCE

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Upper tract transitional cell carcinoma: Diagnostic and therapeutic considerations

Determining grade of disease is important, as nephron-sparing approaches may be feasible.

**Around the Practice** is a monthly urologic virtual tumor board featuring live case review from multidisciplinary experts, presented by *Urology Times*® in partnership with LUGPA. On January 20, 2021, a panel convened to discuss cases involving an incidentally discovered renal mass as well as upper tract transitional cell carcinoma. What follows is an edited portion of the panel’s conversation regarding the upper tract transitional cell carcinoma case.

The panelists included moderator Raoul S. Concepcion, MD, FACS; Jason M. Hafron, MD; Joelle Hamilton, MD; and Jeremy D. Handel, MD.

**CONCEPCION**: In this case, the patient is a 64-year-old White male who presents with a 3-day history of asymptomatic gross hematuria, no voiding complaints, and no history of stones. He was a 2-pack/day smoker for 25 years, and his medical history is otherwise noncontributory. He has a history of colorectal cancer with both his younger brother and father.

The exams are unremarkable. Cytology is nondiagnostic. Office cystoscopy is negative for any type of bladder lesions. The provider conducted an upper tract work-up per guidelines. CT imaging showed a big filling defect in the left renal pelvis. Dr Hamilton, is there a role for genetic testing in this patient?

**HAMILTON**: Yes, there is. The first thing that comes to mind is Lynch syndrome. Lynch syndrome occurs when there is a germline mutation in mismatch repair genes, resulting in loss of mismatch repair proteins MLH1, MSH2, MSH6, or PMS2, which can be detected by immunohistochemistry (IHC). An abnormal test of any of these 4 proteins on IHC suggests possible Lynch syndrome.

Up to 15% to 20% of patients with Lynch syndrome will develop an upper tract urothelial cancer. The urologist can refer a patient to genetic counseling can be done regarding germline testing. A third and less cost-efficient way of testing is IHC of the original pathology. When Lynch syndrome is suspected by the family history as per the Amsterdam Criteria, genetic counseling can be done regarding germline testing. A third and less cost-efficient way is genomic sequencing.

**CONCEPCION**: Dr Hafron, from a diagnostic approach and a therapeutic approach, please walk us through how you would manage this patient.

**HAFRON**: My first step would be to do a ureteroscopy and take a biopsy of the lesion. You need to get tissue. Radiographic images are no longer adequate for any surgical resection. I typically biopsy with a basket. Tissue is king, and with a forceps biopsy, you really don't get good tissue. I will also do a selective cytology. I think that's critical, as well, to further stage the disease. And then I think the issue of pathology becomes very important. It's a new way to look at these lesions because with the advent of newer chemoablative agents, specifically Jelmyto (mitomycin-containing reverse thermal gel), there is potential now for nephron-sparing approaches for treating these lesions.

Historically, we would only consider nephron-sparing procedures for patients with bilateral disease, solitary kidneys, or acute or chronic renal insufficiency. But now, we're starting to see that there is an option for nephron-sparing surgery patients with low-grade disease. Low-grade disease typically represents about 30% of patients who present with upper tract masses. The tissue is very important, and the grade of the tissue is very important. The grade of the tissue in upper tract correlates much better with invasive disease. High-grade in upper tract is considered invasive and I personally consider it to be systemic disease. That's different from bladder, because we know we can get high-grade lesions in the bladder that are noninvasive. High-grade disease is a different disease. If you find a patient with low-grade disease and their tumor is less than 2 cm and they have low-grade selective cytology, you really should consider nephron-sparing approaches.

I think there's a major educational deficit in urology. Not all tumors in the upper tract require a nephroureterectomy; 30% of these patients potentially qualify for nephron-sparing treatment. The critical aspects are the evaluation and the work-up. You really have to make sure that they're truly low-grade disease.

**CONCEPCION**: For this particular case, access should be relatively straightforward, but oftentimes, because we're generally using flexible ureteroscopy, there can be access problems, whether it be because of a body habitus, tortuous ureter, ureteral strictures. What if this was a filling defect, say in a minor calyx, where you cannot get deflection of the scope with your biopsy forceps? Dr Handel, what is the role of percutaneous access to get tissue?

**HANDEL**: I've never heard of this being done specifically. But if there was a unique situation with extenuating circumstances, and no other option was available, I could conceive of a way to do this. To be clear, this would be beyond
the normal scope of practice. I can think of 1 case where I actually did get access for a ureteral mass, and then I ended up doing a biopsy. When we look at percutaneous nephrostomy access, one of the ways we assess cases is dilated versus nondilated. When we’re doing a nephrostomy access for something that has a nondilated collecting system, like a surgical injury or some type of leak or fistulous communication. It is far easier to access in obstruction, where they have a dilated calyceal system.

When we’re trying to get nephrostomy access into a decompressed system, it’s like trying to slide a needle between 2 pieces of paper deep into the belly. That can be pretty challenging. We have several ways to approach that. One is what we call tandem technique, where we intentionally stick a 21-gauge needle centrally knowing full well it won’t be our definitive access. We use it to distend the collecting system. That allows us to visualize and then stick a safe place that we can upsize to a more definitive access.

Another option is to give Lasix and contrast intravenously. There’s a sort of cocktail that is used to provide visualization of the collecting system for access, to give you transient opacification, or just [intravenous] contrast to opacify it.

Once you get access in the collecting system, you would have to maneuver toward the lesion under fluoroscopy. This is the kind of procedure. But if it’s not dilated, that could be tricky; just simply getting access can be a very tricky procedure.

CONCEPCION: Dr Hafron, let’s say pathology comes back with low-grade disease. What are the current therapies that are approved for the management of low-grade upper tract urothelial cancer?

HAFRON: Currently, Jelmyto is the only approved therapy. One of the biggest publications that came out of 2020 was the OLYMPUS trial (NCT02791328) that led to fast-tracked FDA approval of Jelmyto.

This is a chemoablative drug that is instilled as a liquid, but is heated by body temperature to a gel form, delivering about 6 hours of mitomycin in that area. The OLYMPUS trial evaluated Jelmyto in patients with tumor size of 15 mm or smaller. Impressively, 59% of patients had a complete response.

I’ve had a handful of patients that we’ve treated with Jelmyto, and I think it’s going to really improve our care and save a lot of kidneys so that we don’t always have to go to radical nephroureterectomy. We potentially can decrease our recurrence rates with this and potentially minimize progression to invasive disease.

From a diagnostic approach and a therapeutic approach, please walk us through how you would manage this patient.

RAOUL S. CONCEPCION, MD, FACS

My first step would be to do a ureteroscopy and take a biopsy of the lesion. You need to get tissue. Radiographic images are no longer adequate for any surgical resection.

JASON M. HAFRON, MD

In addition, Steba Biotech is conducting a phase 3 trial of padeliporfin (TOOKAD VTP) evaluating that agent for low-grade upper tract urothelial cancer (NCT04620239). The science behind this is fascinating. Basically, the agent is based on algae and is a systemic infusion. After infusion, once the target tissue is exposed to light, this will cause necrosis of the lesion.

What’s critical when using Jelmyto is that these patients still have to be monitored; they still have to have regular ureteroscopy and imaging. Additionally, there was a 44% urethral stenosis rate reported in the OLYMPUS trial. Dr Sarena Matin, who presented long-term data from the OLYMPUS trial at the 2020 Society of Urologic Oncology annual meeting, said that he’s transitioning to placing nephrostomy tubes for instilling Jelmyto, hoping that that will decrease the ureteral stenosis rate. I think we’re probably going to transition to using nephrostomy tubes to instill it was well.

CONCEPCION: Dr Hamilton, what if the pathology comes back as high grade? What is the role of either adjuvant or neoadjuvant therapy?

HAMILTON: I do always like to have sufficient tissue on pathology so that I can have a detailed discussion and shared decision-making with the patient as to whether cisplatin is of benefit to them. What we do know from a meta-analysis is that adjuvant cisplatin increases cancer-specific, disease-free, and overall survival.1 There is also a clinical trial evaluating neoadjuvant gemcitabine-cisplatin versus gemcitabine-carboplatin; however, it recruited very poorly, and the data for that trial are not out yet (NCT02412670).

But when you pool all the data together, there is benefit in overall survival and cancer-specific survival. It is difficult to get patients through, but I have treated patients in the neoadjuvant setting.

ABOUT THE PANELISTS

CONCEPCION is director of the Comprehensive Prostate Center and clinical associate professor of urology at Vanderbilt University School of Medicine, Nashville, Tennessee.

HAFRON is a partner at the Michigan Institute of Urology, PC; an associate professor of urology at the William Beaumont School of Medicine, Oakland University; and the director of robotic surgery at Beaumont Hospital Royal Oak in Michigan.

HAMILTON is an oncologist with Urology Clinics of Alabama in Homewood.

HANDEL is a vascular and interventional radiologist at Beaumont Hospital Royal Oak.

REFERENCE


IN ASSOCIATION WITH
Minimally invasive treatment with the iTind device (Medi-Tate) provided rapid and sustained improvement of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH), without adversely affecting patients’ sexual function, according to a recently published 12-month study.

iTind is an alternative to pharmaceutical management and surgery for relieving BPH-associated lower urinary tract symptoms in men with prostate volumes of less than 75 mL, no obstructive median lobe, a high bladder neck, and good bladder function. Urologists can do the procedure in the office, placing the self-expanding temporary nitinol device in a folded configuration in the prostatic urethra. The device expands during the next 5 to 7 days before urologists completely remove it.

“Current therapies for lower urinary tract symptoms secondary to BPH involve either treating the tissue with some type of energy, whether it is vapor, electrocautery, or laser energy, or applying a permanent implant,” said study author Bilal Chughtai, MD, associate professor of urology at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. “What is novel about the iTind device is it does not deploy energy into the prostate, and it is fully removed. There is nothing left behind after treatment.”

The investigators conducted a randomized controlled study of men 50 years and older, comparing 118 men who received the iTind device to 57 men in the sham control group. Investigators assessed urinary flow rate at baseline, 1.5, 3, and 12 months postoperatively, using the International Prostate Symptom Score (IPSS), peak urinary flow rate, residual urine, quality of life, and the International Index of Erectile Function. Study participants were unblinded at 3 months.

The findings included the following:

- At 3 months, 78.6% of men treated with the iTind device showed a 3 or more point reduction in the IPSS, compared with 60% of men in the sham control arm (Figure).
- At 12 months, the iTind group had a 9.25 decrease in the IPSS, a 3.52-mL/s increase in peak urinary flow rate, and a 1.9-point reduction in quality-of-life score.
- More than 38% of patients in the iTind group experienced adverse events, which were typically mild and transient, compared with 17.5% in the sham control arm.

According to the paper, dysuria occurred in 22.9% of men and hematuria in 13.6% in the iTind arm compared with 8.8% and 0% in the sham arm within the first 30 days.

None of the men in the study experienced de novo ejaculatory or erectile dysfunction.

“This paper demonstrates the safety and efficacy of the iTind device over a 12-month period,” Chughtai said. “Ultimately, what we found was that this treatment with the iTind device did provide substantial improvement in lower urinary tract symptoms without adversely affecting sexual function. And this was done at 16 settings, as well as in the ambulatory surgery setting.”

Results are similar to previous studies

These results were similar to findings from 2 previous single-arm studies on the iTind device conducted in Italy.1,2 Those study results showed the treatment provided rapid and effective relief of lower urinary tract symptoms secondary to BPH for up to 3 years.

Chughtai said the best candidates for the iTind are male patients who are concerned about sexual function and have a prostate volume between 25 and 75 cc, and do not have an obstructive median lobe.

More data are needed to determine whether men with prostates greater than 80 g and those with an obstructing middle lobe are candidates for the therapy.

“The quality-of-life finding in this study is particularly important, according to Chughtai. “When you talk about flow rate and residual urine in the bladder, those are objective measures that we look at to determine the success of a treatment,” he said. “But ultimately, what probably matters more for a quality-of-life condition like lower urinary tract symptoms secondary to BPH or benign prostatic obstruction is how the patients respond and how they feel. If they report a statistically significant and substantial improvement in their quality of life, that is a very important metric for providers and patients because it is saying that these patients are typically happy with the way their urinary symptoms are after treatment.”

Olympus, which holds the exclusive right to distribute the iTind device in the United States, announced the FDA’s de novo classification of the iTind device on April 6, 2020.11

Disclosures: Bilal Chughtai, MD, is a consultant and investigator for Boston Scientific, Olympus Therapeutics, Medi-Tate, and Medeon Bio.

REFERENCES


Benefits of robotic simple prostatectomy may outweigh greater cost

Robotic approach is also associated with a shorter median hospital stay, data indicate

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Robot-assisted simple prostatectomy (RASP) is associated with superior perioperative outcomes compared with open simple prostatectomy (OSP). The differences might justify the marginally higher hospitalization cost of RASP and even translate into overall cost savings, concluded investigators who conducted a comparative analysis of the 2 procedures.1

For the study, investigators used the National Inpatient Sample (NIS) to identify patients who underwent OSP or RASP for benign prostatic hyperplasia (BPH) between 2013 and 2016. It found that compared with the open procedure, RASP was associated with a shorter median hospital stay (2 days vs 4 days), lower overall complication rate (11.1% vs 29.2%), lower rate of blood transfusion (4.3% vs 16.4%), and a greater likelihood of discharge directly to home rather than to a nursing facility (88.9% vs 76.7%; P < .01 for all comparisons).

Hospitalization cost is significantly greater for RASP
The investigators also found that complications were associated with increased hospitalization cost and greater length of stay (LOS). Despite the shorter LOS and lower perioperative complication rate associated with RASP, total unadjusted hospitalization cost was significantly greater for RASP compared with OSP ($13,467 vs $10,855), likely related to up-front operative costs. Cost analysis performed with a multivariable regression model that adjusted for relevant patient and hospital characteristics found that the robotic approach to simple prostatectomy contributed an additional $6175 to the cost model, whereas the cost of each additional day of hospital stay contributed $1687, suggesting that a reduction in approximately 3 to 4 hospitalization days needed to offset costs associated with the robotic system.

“We believe that if a man cannot undergo or cannot find a center that offers transurethral surgery for large prostate glands, robotic simple prostatectomy is a viable alternative with clinical advantages compared with open surgery with a relatively marginal increase in cost,” Bhanvadia added.

RAJ BHANVADIA, MD

RASP is also linked to lower respiratory complication rates
The study included 2551 men in the OSP group and 704 men who had a RASP procedure. A comparison of the characteristics of the 2 cohort results showed that the patients undergoing RASP were significantly younger than the patients undergoing OSP (median age 68 vs 71) and significantly more likely to be obese (11.4% vs 7.2%), and significantly more likely to have no comorbidities (23.2% vs 13.5%). In addition to the differences between the 2 cohorts in rates of overall complications and transfusions, the outcomes analyses showed that RASP was associated with significantly lower rates of respiratory complications, ileus or bowel obstruction, sepsis, and genitourinary complications compared with OSP.

Although other studies have shown that RASP is effective and associated with safety advantages compared with OSP, the comparative analysis conducted by the Southwestern Medical School investigators is one of the first to examine surgical outcomes, length of stay, and cost differences between the 2 procedures in a large US-based population.

“Prior cost studies included a mixed group of approaches, including laparoscopic, had relatively small RASP cohorts, or were single centered and had so far produced mixed results. A major strength of our study relative to others in the literature is that it utilizes a large all-payer national population that includes Medicaid and Medicare patients, with a large number of both OSP and RASP patients included. Additionally, many population-based data sets that could analyze outcomes and costs lack data on all insurance types,” said Bhanvadia.

The investigators acknowledged that major limitations of the comparative analysis were that data were not available for comparing the 2 cohorts with respect to prostate gland size. However, the investigators were unable to break down fixed and variable costs, including operative time and the retrospective nature of the study.

But according to Bhanvadia, perhaps its most important limitation is that it does not compare RASP with holmium laser enucleation of the prostate (HoLEP). “Some studies report advantages of HoLEP compared with RASP, but we were not able to identify HoLEP cases in the NIS due to the limitations of existing Current Procedural Terminology coding,” he said. “Additional studies are needed to provide high-quality comparisons between experienced high-volume robotic centers and high-volume centers specializing in HoLEP.”

REFERENCE
INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 2.5% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 0.8% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 3% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® (see Use in Specific Populations (8.1, 8.3)).

ADVERSE REACTIONS
Adverse Reactions — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (SPARTAN and TITAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
- Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the TITAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)
- Chemistry — In the TITAN study: hyperglycemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (9%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%);
- Immunocomplex-type reactions — In 2 randomized studies (SPARTAN and TITAN), rash was common, occurring in 37% and 38% of patients treated with ERLEADA® and placebo, respectively. Rash was most commonly associated with urticaria or papulo-purpuric rash.

As soon as you diagnose mCSPC or nmCRPC...
INDICATIONS

Cerebrovascular and Ischemic Cardiovascular events

In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Falls

Falls were not associated with loss of balance and gait in patients treated with ERLEADA® in patients who develop a seizure during treatment. It is recommended to establish treatment guidelines and consider use of bone-active agents in patients with nmCRPC.

Fractures

Fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. Evaluate patients for fracture risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Effect of Other Drugs on ERLEADA®

Effect of Other Drugs on ERLEADA®

Concomitant use of ERLEADA® with medications that are substrates of UGT may result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued. Concomitant use of ERLEADA® with medications that may inhibit or inhibit the activity of breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) may result in decreased exposure.

ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; nmCRPC = non-metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; TITAN = Targeted Investigational Treatment Analysis of Novel Androgenics.

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Please see Summary of Full Prescribing Information for ERLEADA® on subsequent pages.


START EARLY WITH ERLEADA®

TO PUSH BACK ON PROGRESSION

In the TITAN study1: 33% reduction in the risk of death1 (ERLEADA® + ADT vs placebo + ADT; median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053)

In the SPARTAN study18: 2-YEAR improvement in median MFS1 (ERLEADA® + ADT vs placebo + ADT; 40.5 months vs 16.2 months; HR=0.28, 95% CI: 0.23, 0.35; P<0.0001)

Students of TITAN were a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or eligible metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a bilateral orchectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the first of any event of first evidence of blinded independent central review–confirmed distant metastasis, defined as new bone or soft tissue lesions, or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of opioid chemotherapy.

§In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph node ≥2 cm in short axis (N1) located below the pubic symphysis at screening were allowed in the study. All patients in SPARTAN had a PSA doubling time ≤10 months at study entry.

mCSPC

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B:21.25”

T:21”

UT0221_026-029_Janssen_FP AD.indd   27

64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.5%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%). Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 76 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 9% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

Drug Interactions

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moiety. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosing and Administration (2.2)).

Drug Interactions

In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Cerebrovascular and Ischemic Cardiovascular events

In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Effect of Other Drugs on ERLEADA® —

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moiety. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosing and Administration (2.2)).
ERLEADA® (apalutamide) tablets

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:
- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, anorexia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28 6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>23 0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>18 0.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

<sup>b</sup> Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatis, and rash vesicular

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (5% versus 6% on placebo), muscle spasm (5% versus 2% on placebo), dysguesia (5% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference >5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27 0.4</td>
<td>19 0.6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrophicicidemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 3</td>
<td>12 2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Does not reflect fasting values
Non-metastatic Castration-resistant Prostate Cancer (nmCRPC) SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, and more commonly from rash (3%). Adverse reactions leading to the interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
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<td>5</td>
<td>6</td>
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<td>Metabolism and nutrition disorders</td>
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<td>18</td>
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<td>16</td>
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</tbody>
</table>

* Includes fatigue and asthenia
* Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
* Includes rash, rash maculopapular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash purpura, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
* Includes appetite disorder, decreased appetite, early satiety, and hypophagia
* Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in ≥2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (8% versus 2% on placebo), and heart failure (2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference ≥ 5% All Grades in SPARTAN (nmCRPC))

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
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<tr>
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<td>Hyperglycemia</td>
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</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67</td>
<td>49</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area (BSA)) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 39% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted [see Drug Interactions].

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apolutamide).

No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability [see Dosage and Administration (2.2) in Full Prescribing Information]. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UGT-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in Full Prescribing Information].
Minimally invasive PCNL outcomes are comparable to surgery, standard PCNL

Further studies are needed to determine the procedure’s role in renal stone disease, investigator says

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Analyses of data collected in a prospectively maintained database support the recommendation for urologists to consider MIP, the minimally invasive version of mini-percutaneous nephrolithotomy (mini-PCNL), for stone removal in patients with medium-sized stones (10-20 mm).

Investigators reported their findings online in the Journal of Endourology. The study included data for 46 patients who underwent the procedure during a period from 2017 to 2019 and had reviewable CT imaging postoperatively. Initial stone size averaged 21.32 mm, measured between 1.9 and 20 mm in 29 patients (63%), and ranged up to 84 mm.

Based on postoperative CT imaging reviewable for 46 patients, 20 patients (43%) were stone-free, defined as having no identifiable fragments seen. Another 5 patients (11%) had residual fragments 0 to 2 mm, 3 patients (7%) had residual fragments 2 to 4 mm, and 18 patients (39%) had residual fragments larger than 4 mm. The stone-free rate for patients with initial stone burdens of less than or equal to 0 mm and greater than 10 to less than or equal to 20 mm was 57% and 52%, respectively, and dropped to 25% for patients with larger stones.

“The MIP procedure, which is performed using a proprietary nephroscope that uses irrigation to assist passage (n = 1913). All patients had confirmed ureteral stones with a width of 2 mm to 9.9 mm. The mean age in the spontaneous passage arm was 51.9 years, 67.4% of patients were male, and 53.5% had a kidney stone. The median stone width was 3.6 mm. The percentage of patients with small stones (<5 mm) averaged 21.5%, moderate (5-6.9 mm), and large (7-9 mm) stones was 52.9%, respectively. Overall, 73.1% of patients had distal stones, and 26.9% of patients had proximal or middle stones. Incidence of hydronephrosis included none (14.7%), mild (57.6%), moderate (25.7%), and severe (2%). Across the subgroup, 38.7% of patients had standing (edema).

In the early intervention arm, the mean age was 51.9 years, 67.4% of patients were male, and 53.5% had a kidney stone. The median stone width was 5 mm. The percentage of patients with small stones (<5 mm), moderate (5-6.9 mm), and large (7-9.9 mm) stones was 76.4%, respectively. Overall, 73.1% of patients had distal stones, and 26.9% of patients had proximal or middle stones. Incidence of hydronephrosis included none (14.7%), mild (57.6%), moderate (25.7%), and severe (2%). Across the subgroup, 38.7% of patients had standing (edema).

For example, reported outcomes with mini-PCNL suggest that it decreases blood loss compared to standard PCNL, but the question of whether the difference is meaningful to patients remains unanswered,” he said. “Our observational study does not provide a direct comparison to another modality with control for key variables that can influence outcomes. Furthermore, because most patients were discharged on the day of surgery, it lacks assessment of commonly reported postoperative hematologic changes.”

These limitations are being addressed in a study undertaken by the Endourology Disease Group for Excellence Consortium. The study is a randomized controlled trial with 6 participating centers that is comparing MIP with standard PCNL and is designed to determine whether the minimally invasive procedure is superior to PCNL for minimizing operative blood loss.

Disclosures: Roger L. Sur, MD, and Seth Bechis, MD, are consultants for Karl Storz.

REFERENCE

Which patients with ureteral colic benefit most from early surgical intervention?

Jason M. Broderick
Associate Editorial Director, Urology Times®

Research published in the Journal of Urology identified the ideal patient population to receive early surgical intervention for acute ureteral colic.

Using multivariable regression of patient data, the investigators concluded, “Early intervention improves outcomes for patients with large (>7 mm) ureteral stones or to 7 mm proximal or mid ureteral stones.” However, they also noted, “early intervention may increase morbidity for patients with stones smaller than 5 mm.”

Using administrative data and structured chart review, the investigators compiled a study population of 3081 patients with acute ureteral colic. The patients had been seen at 9 emergency departments across 2 Canadian provinces and underwent either early surgical intervention (n = 1168) or spontaneous passage (n = 1913). All patients had confirmed ureteral stones with a width of 2 mm to 9.9 mm.

The mean age in the spontaneous passage arm was 49.7 years, 73.2% of patients were male, and 44.5% had a kidney stone. The median stone width was 3.6 mm. The percentage of patients with small stones (<5 mm), moderate (5-6.9 mm), and large (7-9 mm) stones was 76.4%, respectively. Overall, 73.1% of patients had distal stones, and 26.9% of patients had proximal or middle stones. Incidence of hydronephrosis included none (14.7%), mild (57.6%), moderate (25.7%), and severe (2%). Across the subgroup, 38.7% of patients had standing (edema).

In the early intervention arm, the mean age was 51.9 years, 67.4% of patients were male, and 53.5% had a kidney stone. The median stone width was 5 mm. The percentage of patients with small stones (<5 mm), moderate (5-6.9 mm), and large (7-9 mm) stones was 76.4%, 19%, respectively. Overall, 73.1% of patients had distal stones, and 26.9% of patients had proximal or middle stones. Incidence of hydronephrosis included none (14.7%), mild (57.6%), moderate (25.7%), and severe (2%). Across the subgroup, 38.7% of patients had standing (edema).

“Which patients with ureteral colic benefit most from early surgical intervention?” says.

See EARLY INTERVENTION page 31
Mirabegron may improve erectile dysfunction in men with OAB symptoms

Findings support continued investigation of treatment in men with overactive bladder and ED

Andrew D. Bowser
Urology Times® Correspondent

Treatment of overactive bladder (OAB) with a β3-adrenoceptor agonist may also improve erectile dysfunction (ED) in men who have symptoms of both disorders, according to study results reported at the 2020 Sexual Medicine Society of North America (SMSNA) 21st Annual Fall Scientific Meeting.1

Five of 13 men with OAB and mild to moderate ED experienced clinically relevant increases in erectile function after 12 weeks of treatment with mirabegron (Myrbetriq), a β3-adrenoceptor agonist approved by the FDA for treatment of OAB. As expected, symptoms of OAB also improved, with no serious adverse events (AEs) noted over 12 weeks, said Serkan Karakus, MD, a clinical fellow with the James Buchanan Brady Urological Institute at Johns Hopkins School of Medicine in Baltimore, Maryland.

“This is a single-arm, observational study and small study group, but we found some promising results,” Karakus said. “So I think we could move forward to larger, randomized studies.”

These preliminary findings at least suggest that mirabegron could be an alternative for ED treatment when phosphodiesterase type 5 (PDE5) inhibitor treatment fails or is contraindicated, according to coinvestigator Arthur L. Burnett II, MD, MBA, a professor of urology at Johns Hopkins School of Medicine.

“The question is whether have we solved ED treatment entirely with PDE5 inhibitors, and the answer is no,” Burnett said in an interview. “So why not explore alternative mechanisms with a thought that this new therapy, which may not necessarily be addressing a predominant mechanism of penile erection, could still be a complementary or additive therapy to consider.”

In his SMSNA presentation, Karakus described OAB and ED as disorders of the lower genitourinary tract that share several pathophysiologic mechanisms, including dysregulation of the nitric oxide-cyclic guanosine monophosphate pathway, increased sympathetic tone, upregulation of Rho kinase expression, and chronic hypoxia.

The β3-adrenoceptor has been found in human corpus cavernosum, he added, noting that mirabegron could act simultaneously in the bladder and corpus cavernosum via β3-adrenoceptor activation.

The nonrandomized, single-arm study by Karakus and colleagues included 20 men with OAB and mild to moderate ED as defined by International Index of Erectile Function (IIEF) Erectile Function domain scores between 11 and 25 or Sexual Health Inventory for Men (SHIM) scores between 8 and 21. Patients received mirabegron 25 mg daily for 2 weeks and then 50 mg daily for the next 10 weeks.

Seven patients were lost to follow-up, and 13 remained in the study for the full 12 weeks, according to investigators. Treatment with mirabegron was associated with significant improvements in mean SHIM scores through week 4 and week 8 (P = 0.0003). The SHIM score decreased slightly by week 12, so no significant improvement was noted at that time, according to Karakus.

However, looking at individual SHIM scores, 5 of 13 patients experienced a 4-point increase at 12 weeks, and there were no clinically relevant decreases in SHIM or IIEF scores for any patient. IIEF scores trended toward significant improvement at week 4 and week 8 evaluations (P = 0.08), and no changes were seen in orgasmic function or sexual desire.

As anticipated, treatment with mirabegron significantly improved symptoms of OAB and OAB-related quality of life, according to the investigators. In addition, no serious adverse events were observed; transient nonserious AEs included headache, constipation, back or leg pain, flulike symptoms, rash, and elevated blood pressure, Karakus said.

According to Burnett, senior author of the study, these findings support continued investigation of the safety and efficacy of mirabegron in men with OAB and concurrent ED.

“This is not a definitive study, it’s not a randomized controlled trial, and the numbers aren’t there that need to be done,” Burnett said. “But I think it does provide some interesting initial observations to test the hypothesis and possibly will be a foundation to move forward with something more rigorous to come.”[5]

Disclosure: Astellas Pharma US, Inc, provided funding for the study.

REFERENCE

“Our recommendations apply as an initial approach to patients with ureteral colic, and not to those already failing a trial of passage. Future studies should assess the impact of ureteral stents in stone subgroups, the modifying effects of pharmacological treatments, as well as cost-effectiveness and patient reported outcomes for patients having early intervention versus spontaneous passage,” the investigators wrote in their conclusion.[5]

REFERENCE

EARLY INTERVENTION

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had stranding (edema).

These data showed that “intervention patients were older, more often female, and had larger more proximal stones with more prominent hydroureterephrosis,” the investigators wrote.

The primary outcome measure for the study was treatment failure, which the trial design defined as the need for intervention or hospitalization within 60 days. The key secondary outcome measure was emergency department revisit rate.

Among the group with stones 7 mm or larger, 34.7% of patients with early intervention experienced treatment failure compared with 58.6% with spontaneous passage (risk difference, 23.9%). Emergency department revisit rates were similar in the large stone group, regardless of whether or not a patient received early intervention.

In patients with medium-sized stones of 5 mm to 6.9 mm in width, those receiving early intervention had a lower treatment failure rate than those in the spontaneous passage group, at 37.4% versus 55.5% (risk difference, 18.1%), respectively, if the stones were located in the proximal or middle ureter. In contrast, early intervention led to more treatment failures and emergency department visits versus spontaneous passage in patients with stones less than 5 mm in width. The treatment failure rates and emergency department visit rates were 31.5% versus 9.9 and 38.5% versus 19.7%, respectively.

“Which patients should have early surgical intervention for acute ureteral colic?” J Urol. 2021;205(1):152-158. doi:10.1097/JU.0000000000001018

FEBRUARY 2021 | Urology Times® | 31
Investigators evaluate retention after sling surgery for post-RP incontinence

Cheryl Guttman Krader, BSPharm
Urology Times® Correspondent

Acute urinary retention is not uncommon among men who undergo placement of a proprietary transobturator sling (AdVance) for management of postprostatectomy stress urinary incontinence. Still, it is rarely persistent, and it is not predicted by findings from preoperative urodynamic studies, according to the results of a recent retrospective study.1

“Urodynamic studies are often performed prior to surgical intervention for postprostatectomy stress urinary incontinence, but their ability to predict urinary retention following male sling placement is unknown,” said Eric S. Rovner, MD, study investigator and professor of urology, Medical University of South Carolina, in Charleston.

“The results of our study, which to our knowledge is the largest to date to assess postoperative urinary retention following AdVance Sling placement, suggest that if urodynamic studies are being done preoperatively only with the aim of predicting retention, then this investigation is probably not needed. Nevertheless, urodynamic studies still have a role if their purpose is to assess other issues, such as filling abnormalities,” he told Urology Times®.

The study included 391 patients who underwent placement of the AdVance sling during the years 2007-2019. Approximately three-fourths of the patients (n = 303, 77.5%) had preoperative urodynamics performed. Median follow-up for the entire cohort was 18.1 months.

Acute urinary retention, defined as an inability to urinate or elevated postvoid residual (PVR) after the first removal of the urethral catheter resulting in an invasive intervention, occurred in 55 (14.1%) men. The majority of those patients were recatheterized (87%), and the rest were treated with clean intermittent catheterization.

Three-fourths of the patients with acute urinary retention had resolution of the problem by their second postoperative visit. Among the 13 patients whose urinary retention persisted, 6 patients, representing 1.5% of the total cohort, had chronic urinary retention at their last follow-up visit. All 6 men were being treated with clean intermittent catheterization.

Comparisons of the preoperative characteristics in the groups with and without acute urinary retention showed no statistically significant differences in their demographics, comorbidities, previous interventions, radical prostatectomy approach, or incontinence severity. Within the subgroup that had urodynamics studies, there were no significant differences between men with and without acute urinary retention in average maximum flow rate (Qmax), detrusor pressure at Qmax (PdetQmax), PVR, bladder contractility index (calculated using the formula PdetQmax + 5 x Qmax), or presence of impaired contractility (defined as BCI <100).

Mean time to initial catheter removal was significantly shorter in men who developed acute urinary retention than in those who did not (2.8 vs 4.6 days; P = .002). In a univariate regression analysis, earlier postoperative catheter removal was the only explored factor that independently predicted postoperative acute urinary retention. The risk was 17% lower in men whose urethral catheter was removed in less than 2 days after the sling procedure compared with the group that had an earlier void trial (P = .003).

“Neither impaired bladder contractility nor abnormal voiding detrusor activity (absence of detrusor contraction during pressure flow, presence of Valsalva voiding or low detrusor pressure at maximum flow) were predictive of acute urinary retention following sling placement,” Rovner said.

Rovner noted that the study has several strengths. These include its multicenter design, a large patient population with a significant proportion of men who had preoperative urodynamics studies, and significant follow-up time.

But the study also has limitations, some of which are inherent to both its retrospective and multicenter design. Additionally, the version of the male sling that was the focus of the study is no longer commercially available.

“Preliminary work suggests that the urinary retention rate following placement of the currently marketed AdVance XP Male Sling System may be slightly higher than the version used in our study. The difference is speculative, however, because there are no direct comparisons,” Rovner said. “It would be worthwhile, therefore, to conduct a prospective study of retention following placement of the newer version of the sling.”

REFERENCE

Anticholinergic use for 3 months or longerraises dementia risk by about 46%

Lisette Hilton
Urology Times® Correspondent

Anticholinergic use for 3 months or longer increases dementia risk by about 46% compared with nonuse, according to a recent review and meta-analysis published in Neurourology and Urodynamics.1 The investigators of the review saw a similar relationship with drugs many urologists use to treat overactive bladder.

According to study author Roger R. Dmochowski, MD, MMHC, professor of urologic surgery at Vanderbilt University Medical Center, the increased risk of incident dementia following anticholinergic agent use is not well known or understood. But he said that urologists and other prescribers, as well as patients, are becoming more aware of the risk. This paper sheds light on the significant separation in cognition and other central nervous system risks in patients taking anticholinergic medications versus those who are not, he said.

In the main analysis, the investigators did a systematic literature review and meta-analysis assessing the impact of anticholinergic use for 3 months or longer on the risk of multiple subtypes of incident dementia. It also evaluated the association between drugs used to treat overactive bladder and dementia risk.

Although the electronic search revealed more than 2100 articles for the main analysis, only 6 studies met the inclusion criteria. These 6 papers assessed anticholinergic agent impact, reflecting outcomes for dementia subtypes, including Alzheimer disease, Lewy body dementia, vascular dementia, and others.

See DEMENTIA page 33
Proof of “obesity paradox” in kidney cancer continues to grow

Large review of RCC trials corroborates prior studies linking higher BMI with improved prognosis

The data for the trial were pooled from 34 publications compiled from a computerized search of the MEDLINE, Embase, ProQuest, PubMed, and Google Scholar databases.

Mechanism behind the paradox remains unknown

The investigators wrote that the specific mechanism of how obesity might improve outcomes in patients with RCC remains unknown; however, they shared several theoretical explanations:

• Patients with a higher BMI are more likely to receive medical testing for other reasons and may be more likely to have an incidental renal mass diagnosed at an earlier stage.
• Some research has demonstrated a more favorable tumor biology in obese patients, specifically shown by downregulated expression of metabolic and fatty acid genes that are a key component of tumor growth.
• The role of adipose tissue at the molecular level is also considered a factor.

The investigators listed several limitations to their analysis, including “the retrospective design of the study, the small sample size, the different techniques used for BMI calculation, and the potential for selection bias.”

Accordingly, the investigators recommended additional research into the fundamental biological mechanisms of the BMI paradox to determine the true significance of BMI on outcomes in patients with RCC.

Summarizing the findings in an accompanying editorial, Alp Tuna Bek sac, MD, wrote, “While this study might not have an immediate impact on current day practice, hopefully, it will encourage researchers to focus on understanding the biological mechanisms of this paradox to further understand RCC, and help individualize RCC treatment in the future.”

REFERENCES

DEMENTIA
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Jason M. Broderick
Associate Editorial Director, Urology Times®

A large systemic review of renal cell carcinoma (RCC) trials has provided additional evidence of the “obesity paradox,” the phenomenon of patients with elevated body mass index (BMI) having a more favorable kidney cancer prognosis, including a survival advantage.1

The review of data from 50,717 patients showed that cancer-specific survival was improved in overweight and obese patients with RCC compared with patients with normal BMI (HR, 0.85). Similar patterns were observed with progression-free survival (HR, 0.68) and overall survival (HR, 0.66). Conversely, underweight patients had inferior cancer-specific survival outcomes compared with overweight/obese patients (HR, 2.16).

The results of this analysis corroborate several prior studies demonstrating a link between higher BMI and improved prognosis in patients with RCC.

“This is the largest systematic review evaluating the potential phenomenon of the obesity paradox in kidney cancer outcomes. It demonstrated a favorable effect of body mass index on kidney cancer outcomes,” wrote the investigators, led by Lawrence Kim, MBChB, of Westmead Hospital, New South Wales, Australia.

The investigators listed several limitations to their analysis, including “the retrospective design of the study, the small sample size, the different techniques used for BMI calculation, and the potential for selection bias.”

Accordingly, the investigators recommended additional research into the fundamental biological mechanisms of the BMI paradox to determine the true significance of BMI on outcomes in patients with RCC.

Summarizing the findings in an accompanying editorial, Alp Tuna Bek sac, MD, wrote, “While this study might not have an immediate impact on current day practice, hopefully, it will encourage researchers to focus on understanding the biological mechanisms of this paradox to further understand RCC, and help individualize RCC treatment in the future.”

REFERENCES
What is the status of chronic condition code G2211?

Recent legislation appears to have delayed implementation of new code

**Q:** I read that G2211 was delayed by 3 years. Can you explain?

**A:** The 2021 Medicare Physician Fee Schedule (MPFS) Proposed Rule included the new Healthcare Common Procedure Coding System (HCPCS) add-on code GCP1X, used to better describe the work associated with visits that are part of ongoing, comprehensive primary care, and/or visits that are part of ongoing care related to a patient’s single, serious, or complex chronic condition. This code could be used by specialists such as urologists who manage complex chronic conditions and may be added to any outpatient evaluation and management service level (99202-99215). This code was resequenced as G2211 in the final rule, released on December 1, 2020. Code G2211’s description reads, “Visit complexity inherent to evaluation and management associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient’s single, serious condition or a complex condition.” This code was valued at 0.33 work relative value units, with a payment of around $16. However, on December 27, 2020, the Consolidated Appropriations Act was passed, which made a number of changes, including a 3.75% increase in MPFS payments for the calendar year 2021, a continued suspension of the 2% payment adjustment (“sequestration”) through March 31, 2021, and a delay of implementation of the G2211 until 2024.

What does this mean? Because of the sheer volume of use of G2211 that was expected to be utilized by providers, these dollars went back into the conversion factor. The Centers for Medicare & Medicaid Services (CMS) therefore recalculated the conversion factor to $34.89. This updated conversion factor represents a 3.3% drop instead of the 10.2% drop included in the final rule.

Those who were expected to be significantly impacted by the greater than 10% drop in the conversion factor, such as those who provide a significant number of surgical procedures over office visits, were subject to a reprieve. Urology as a specialty is not expected to be adversely expected. The American Medical Association has projected the same 8% increase in overall revenue for urology in 2021 over 2020. CMS had not yet issued its projections as of the writing of this article.

Medicare released an updated relative value unit (RVU) file on December 29, 2020, and an updated RVU file on January 5, 2021. Code G2211 was not included in either file.

**Q:** I read your post titled, “What are the documentation requirements for COVID-19 CPT code 99072 for your urology practice?” You stated, “You do not need to link the code to a particular diagnosis code such as ICD-10-CM U07.” Would you expound on that?

**A:** CPT code 99072’s description reads, “Additional supplies, materials, and clinical staff time over and above those usually included in an office visit or other nonfacility service(s), when performed during a public health emergency, as defined by law, due to respiratory-transmitted infectious disease.” As of the writing of this article, the current coronavirus disease 2019 (COVID-19) public health emergency is set to expire on April 21, 2021. CPT code 99072 can be linked to any international classification of diseases (ICD)-10 code used for the office or other outpatient evaluation and management service or other urology CPT code; it does not have to be linked to an ICD-10 code specific for a virus. The code was developed to help physicians offset the costs of supplies, time, and overhead required for all patients coming to the office during the pandemic.

Unfortunately, we have found that most if not all insurers do not pay for this code and additionally often have policies against charging patients for extra supplies, and balance billing would be a violation of their contract. You may attempt to report the code if your office is taking extra steps and purchasing extra supplies to maintain COVID-19-safe protocols; however, you may find that payers not only will not pay but may not process claims with this code reported. If you have already attempted to report the code and have not been reimbursed or seen rejections of claims outright, the problem is not diagnosis code-related but related to the status of the code for the payer, usually bundled.

**Q:** I read your post titled, “What are the documentation requirements for code 517907?” It was very helpful. I would also like to know which Common Procedural Terminology (CPT) code we would use for a post-void residual done without ultrasound.

See G2211 page 36
In this iPub®, Dr. Gordon Brown and Dr. Phillip M. Pierorazio:

Discuss the recent guidelines updates that have expanded the recommended use of kidney-sparing procedures.

Explain the current limitations of radical nephroureterectomy and endoscopic management.

Review the results of a pivotal trial that evaluates the efficacy and safety of a primary tumor therapy for low-grade upper tract urothelial cancer (LG-UTUC).

Describe the first and only FDA-approved treatment for LG-UTUC.

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Gordon Brown, D.O.
Program Director of Urologic Surgery
Rowan University
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New Brunswick, NJ

Phillip M. Pierorazio, M.D.
Associate Professor of Urology and Oncology
Johns Hopkins University
Baltimore, MD
COVID-19 has a greater impact in areas with high income inequality

Infection rates are higher in counties with higher income inequality, data indicate.

**KEITH A. REYNOLDS**

Reynolds is an associate editor for *Medical Economics*.

Evidence continues to mount that the coronavirus disease 2019 (COVID-19) pandemic is disproportionately affecting communities with higher income inequality.

According to a study of all but 1 county in the US during the first 200 days of the pandemic, there were positive associations between COVID-19 incidence and mortality rates with racial or ethnic composition and with income inequality. There was also a joint association of incidence and mortality with both factors.

The investigators found that a 1% increase in income inequality in a county corresponds to a 2% increase in risk of COVID-19 infection and a 3% increase in risk of mortality. The effect was compounded in communities with higher proportions of African American or Latin Americans.

A news release on the study said that the lead author, Tim Liao, PhD, head of the sociology department at the University of Illinois Urbana-Champaign, began the study after noticing a lack of focus on the role of income inequality that has played in the pandemic.

"We needed actual data to really fully understand the social dimensions of the pandemic."

**TIM LIAO, PHD**

"We needed actual data to really fully understand the social dimensions of the pandemic," Liao said. "We knew all along that racial inequality was important, but most of the time people were missing the more complete picture, which includes economic inequality."

The investigators concluded that COVID-19 surveillance systems should account for county-level income inequality to give more light to the social patterning of incidence and mortality because income inequality may harm population health.

"Many studies have concluded that COVID-19 has revealed the fault lines of inequality in the United States," the investigators wrote. "This study expands that picture by illustrating how county-level income inequality matters, in itself and through its interaction with racial/ethnic composition, to systematically disadvantage Black and Hispanic communities."

**REFERENCES**


G2211

continued from page 34

**A:** To best answer your question, we would need to know a bit more specifically what is meant by “without ultrasound.” Do you mean by catheter, or do you mean a handheld device that detects the bladder volume? CPT code 51798’s description reads, “Measurement of post-voiding residual urine and/or bladder capacity by ultrasound, non-imaging.” Therefore, whether the bladder is actually imaged, and the volume calculated or a non-imaging device is used to give a bladder volume, the code can be used. If one performs a bladder catheterization to obtain the post-void residual, use CPT code 51701 (Insertion of non-indwelling bladder catheter [eg, straight catheterization for residual urine]).

**Q:** Can CPT 52601 be coded more than once per patient?

**A:** CPT code 52601 (Transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete [vasectomy, meiotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotyomies are included]) still has a “once in a lifetime” restriction. If a subsequent transurethral resection of the prostate is performed, use CPT code 52630 (Transurethral resection; residual or regrowth of obstructive prostate tissue including control of postoperative bleeding, complete [vasectomy, meiotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotyomies are included]).

Unfortunately, we have found that most if not all insurers do not pay for [CPT code 99072] and additionally often have policies against charging patients for extra supplies, and balance billing would be a violation of their contract.

**SEND US YOUR QUESTIONS**

Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o *Urology Times*, at urology.times@mmhgroup.com. Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

**REFERENCES**

Start your financial year right with these 8 priorities

Look at ways to reduce high-interest debt, and consider contributing to an IRA

**Q:** What are some planning priorities I can implement at the beginning of the year to put myself on a good financial path?

**A:** As we welcome 2021 and try to put 2020 far into the rearview mirror, it is always a good idea to put plans in place for succeeding financially throughout the year. Each year, I provide a checklist to get you started. There are certain to be other things you will want to address; however, getting these 8 financial priorities in place is a good start.

1. **Set short- and long-term financial goals.** Whether you want to be debt free in 10 years or own a home in 3, you are more inclined to save if you have specific goals. Factor these goals into a budget and figure out where you can find the extra money to make them realities.

2. **Budgeting.** Every effective financial plan starts with a budget. Identify necessary spending and savings items. Give yourself a little leeway, but try to stay disciplined with your budget.

3. **Emergency funds.** These can be a financial lifesaver. A sudden job loss, major surprise expense, or unexpected health issue can quickly change your financial picture. The general rule of thumb is to maintain an emergency fund equal to 3 times your monthly living expenses for a dual-income household and 6 months for a single-income household or if 1 person’s income is relied upon to provide for a family’s standard of living. During the coronavirus disease 2019 pandemic, it is a good idea to bolster these funds with 1 or 2 extra months of savings.

4. **Debt reduction.** Look to see whether you can pay off some high-interest debt (like credit cards). With interest rates near record lows, putting extra money toward low-interest debt may not be the best idea. If you think you can earn a higher rate of return than the interest being charged on your debt by investing that extra money, in the long run you should go out ahead. Some forms of debt, such as a mortgage on a house, may also be acceptable because the interest may be tax deductible.

5. **Retirement plan contributions.** If you already contribute to an employer plan such as a 401(k) or 403(b), keep it going. The Internal Revenue Service left the maximum contribution amount unchanged from 2020 at $19,500 ($26,000 for those over age 50). The aforementioned plans should be maxed out before utilizing other tax-advantaged retirement accounts because they are protected by federal law if you are ever sued and have a judgment against you. If you own your practice, determine whether you are utilizing the best type of retirement plan for your specific situation.

6. **Traditional and Roth individual retirement accounts (IRAs).** If you are already maxing out employer-provided retirement accounts and wish to save additional amounts toward retirement, consider contributing to a traditional or Roth IRA. These accounts also offer excellent tax-advantaged growth and are protected in most states from lawsuits. The contribution limit remained unchanged at $6000 per year for 2021 ($7000 if over age 50). Please note that deductibility or availability to contribute is determined by your income, so it is important to be aware of the limitations.

7. **Disability and life insurance.** Often overlooked, disability and life insurance are very important components of financial security. Disability insurance supplements a portion of your income if you are sick or disabled and unable to work. In the event of a long-term disability, it could ensure you stay in your home and/or remain able to save for financial goals like retirement. All eligible physicians should have comprehensive disability coverage that provides at least 60% of their predisability income. Life insurance is slightly more situational, but if you own a home with a mortgage or have any other debts that would not be absolved at your death, have children whose college educations you would want to provide for in the event of your death, then life insurance should be considered.

8. **Estate planning.** The complexity of an estate plan may vary based on your assets and needs, but having basic estate planning strategies is important. Work with an estate planning attorney to review whether you need wills, powers of attorney, trusts, etc.

These are important priorities to have in place and will give you a good foundation to start moving toward a financially secure future. We recommend speaking with your financial adviser about other areas that could use improvement.

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WYOMING
Real-time patient access to charts raises potential for misinterpretations

Here’s how viewing notes in draft form can lead to misunderstandings

I’m not trying to hide anything. I’m really not. I have no problem with patients seeing everything in their chart. It is their medical record, after all. But I do think there should be some limitations on this access.

A surgeon I know was recently working near a major blood vessel and damaged it; things happen in the operating room despite our best efforts. The surgeon did the right thing, controlled the bleeding, and in the process asked a vascular surgeon for help. After the vascular surgeon completed her work, the first surgeon finished the case, brought the patient to recovery, entered some orders in the computer, and then went to talk to the family. And the family was angry. Really angry. What happened? It turns out the family was monitoring the chart during the case and saw the vascular surgeon’s draft operative note before either surgeon had a chance to talk to the family.

I have no problem with patients seeing everything in their chart. It is their medical record, after all. But I do think there should be some limitations on this access.

A vegan patient of mine on testosterone replacement had a slowly rising hemoglobin level. Eventually, he started giving blood to the American Red Cross quarterly. We continued to monitor his labs and I started monitoring his ferritin level. Every medical student knows that chronic blood loss can lead to anemia secondary to iron deficiency. The patient called, angry that I was ordering unnecessary labs as we had never monitored ferritin level in the past.

In December 2016, the government signed the 21st Century Cures Act into law. As part of that law, the federal government mandated that health care providers offer patients free access to the medical records to include consult notes, discharge summaries, history and physical, labs, pathology reports, imaging reports, clinic/procedure notes, and all operating/procedure notes. There are a few exceptions, including psychotherapy notes and notes that might reasonably be assumed to be used in a civil or criminal case. And importantly, most systems are interpreting this law to mean near-real-time access to these records, including all notes in their draft form.

I tend to speak quickly and quietly. You might say I mumble. (You’d be right.) The number of errors I find in my draft operative notes is high and has only gone up since I’ve started wearing an N95 when I dictate. I approached some of the hospital administrators about this potential issue and their response was that I should use premade templates for my procedures (“dot phrases” in the lingo of the hospital EMR). Further, they suggested that I stop dictating completely (a very expensive habit, I was told) and instead simply type. I believe that every case is different and hence my notes should reflect those differences, and much to the administrators’ chagrin, I informed them that I am not a typist. Sorry.

Or we could not provide access to patients to notes in their draft form; they are, after all, in their draft form. Chuckle. Laugh. Get back to work, little cog.

The philosophy of “Open Notes” has been around for decades. Leaders in the field believe that providing real-time access to notes improves patient safety and patient engagement.1 I don’t disagree with those statements, but I do believe that the information patients are provided should be vetted and finalized before being published.1

REFERENCE

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Do you prefer dusting or basketing for removing stones?

I like a combination. Dusting creates less risk of injuring the ureter, reducing fragment size, so they don’t get stuck. It’s nice to have pieces for analysis so you can determine composition and figure out what to do in terms of prevention. Also, information is power, and most patients want to know the type of stone they have. Often, I dust as much as I can, basketing a small fragment to analyze. Fragments left after dusting sometimes aren’t always large enough to grab. Dusting is easier because it allows those fragments to pass without damage to the ureter.

Location makes a difference, however, especially if you have a larger stone up in the renal pelvis. Those are more amenable to dusting because no one wants to make a lot of trips up and down the ureter removing fragments.

Everything comes down to patient selection and location of the stones. If it’s a smaller stone in the lower ureter, basketing it and pulling it out may be quicker than dusting it.”

T. Casey McCullough, DO, MBA, FACOS / Johns Creek, Georgia

I’m doing a lot more dusting. I do a hybrid, but because we have a new-generation laser, the dusting really changed and became a lot faster. I work in 2 hospitals. Last year, we got a new holmium at one, then we got a thulium laser at the other. They’re both much faster than what I had before. They use much higher frequencies to dust.

I’ll still do a hybrid at times. If it’s a distal stone, I’ll out basket it because then I know for sure it’s completely out. If I have a ureteral access sheath, I’ll basket, easily removing everything.

You can reliably basket everything; then, you’re guaranteed to have 100% stone clearance rate. With an access sheath, you can go in and out of the kidney easily and get everything out.

I try to leave a fragment for stone analysis if I can, but I recently had a case with this new laser where I dusted, put a basket in, and nothing came out. I wasn’t able to get a stone analysis, but we can always do a 24-hour urine, so it’s not a terrible loss.”

Roger Yau, MD / Matthews, North Carolina

I prefer dusting. With basketing, stones can still get stuck or create tears in the ureter, whereas if you dust the stone, you can blow the pieces out more gently.

We probably all do some sort of combination, dusting the stone down until it’s an appropriate size where there won’t be tuggering and pulling, and you can basket it through the ureter without scraping the sides.

The location of the stone also helps determine the technique choice. If it’s small and up in the kidney, you may basket it and know you’ve gotten it, whereas if the stone is already stuck in the ureter, you know you’ll have to laser it before basketing.

There are potential problems relying on just 1 method. Just dusting risks leaving microparticles that can form a new stone, and it’s a bit more time-consuming, whereas with the basket, it’s gone. But you have to ensure you can get through the entire ureter without pulling or scraping if you’re just basketing.

Although it’s nice to have a sample to determine the stone’s composition, patients can make different stones every time, depending on what’s going into their urine. So although the composition is important, doing the 24-hour urine test to advise the patient on dietary measures is really more important. So I don’t always treat the patient on a basketed sample anyway.”

Jennifer Linehan, MD / Santa Monica, California
Did patient negligence result in prostate cancer diagnosis?

Provider says the patient failed to timely return for follow-up

A 71-year-old man was seen by his primary care provider for a prostate-specific antigen (PSA) screen on December 5, 2011. The result was a level of 5.33. The patient’s primary care physician referred him to a urologist.

On April 5, 2012, the patient presented to the urologist for the elevated PSA. The urologist performed a history and physical exam. The urologist believed that the patient’s modestly elevated PSA was secondary to an enlarged prostate, otherwise described as benign prostatic hyperplasia (BPH). The patient was given some medication and told to return in 90 days for a repeat PSA study.

The patient did not return to the urologist until December 5, 2013. By that time, the patient’s primary care provider had repeated PSA studies in August 2013 and again in October 2013, which returned at levels of 6.67 and 5.8, respectively. At the second visit, the urologist discussed a microwave procedure to shrink the prostate. The urologist relied on the patient’s description that the values were initially high and then fell back slightly, but no repeat PSA study was performed. The urologist placed the patient back on finasteride and told him to return in 90 days.

Microwave procedure is performed

The patient returned to the urologist a third time on April 16, 2014, and reported that his underlying urological problems had worsened. The urologist did not get a repeat PSA but concluded that the patient’s symptoms were caused by BPH. The urologist’s office subsequently carried out a microwave procedure on May 21, 2014, and told the patient to return for a follow-up. The patient never saw that urologist again.

In September 2014, the primary care provider obtained a PSA that reported out at level 8.8. The primary care provider advised the patient to see a urologist again.

In February 2015, the patient saw a second urologist who performed a PSA test, which returned at level 37. A biopsy proved prostate cancer, with a Gleason score of 7. Further evaluation and imaging studies in March 2015 revealed widespread metastatic disease to the ribs, sacrum, and spine. He ultimately received a diagnosis of stage IV terminal prostate cancer.

The defendant-urologist argued that by not returning 90 days after the initial visit in April of 2012, he was deprived of finding out how the patient’s PSA did while the patient was on finasteride.

The patient sued his first urologist, claiming medical malpractice. He claimed that the urologist was negligent for not doing a repeat PSA test and not offering a biopsy at any time. The urologist denied negligence and further denied that anything he did or failed to do caused the patient’s metastatic cancer.

At trial, the patient-plaintiff contended that he would have been completely curable with timely diagnosis and treatment. However, the jury heard testimony that the patient’s life expectancy was approximately 18 to 24 months.

The defendant-urologist argued that by not returning 90 days after the initial visit in April 2012, he was deprived of finding out how the patient’s PSA did while the patient was on finasteride.

Experts for the defense testified that when a PSA is elevated secondary to BPH, typically cuts the PSA in half and that when the PSA does not fall, despite a patient taking finasteride, urologists strongly consider prostate cancer as an alternative explanation for the abnormal PSA. The defendant-urologist thus contended that if the patient had returned within a reasonable amount of time, it was likely that the PSA would have been unchanged because it was still in the 5 to 6 range in August 2013 and October 2013. All experts at trial agreed that as of April 2012, the patient likely had cancer for years. But because the patient did not timely return after the initial urology visit, the urologist did not have an opportunity to conduct a PSA, offer a biopsy, or otherwise evaluate the patient.

Following an 8-day trial, the jury deliberated for 1.5 days, and returned a defense verdict for the urologist, finding no negligence.

LEGAL PERSPECTIVE: Many states recognize the defense of contributory negligence in medical malpractice cases. Disregarding a doctor’s orders can be patient negligence. Failing to provide an accurate patient history may also constitute patient negligence. In this case, the defendant-urologist could argue that the plaintiff-patient was negligent for failing to timely return for a follow-up. The jury weighed and considered this evidence in deliberations, which likely affected their defense verdict.
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I am a patient.

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*Dr. Cohen is a paid consultant of NeoTract|Teleflex. Results may vary.

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